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PATHWAYS OF MEDICAL PROGRESS[1]

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ON occasions such as this we gather together from laboratories and hospitals as disciples of scientific medicine. We assemble, primarily, for the purpose of exchanging views on problems which seem to have crystallized for each of us individually. Current reviews thus prepared by thoughtful minds and representing diverse perspectives afford those engaged in other fields an opportunity to keep in touch with the trends of contemporaneous research in specialized fields.

But these occasions have other functions, too. The frank exchange of opinions and the exposition of facts upon which they are founded serve to re-energize us, even if like opposite charges they outwardly seem to repel. As no effective electrical forces can exist without positive and negative charges, so no dynamic forces can be induced in research without a polarity of opinion. Furthermore, we who, despite earnest efforts, frequently become dissatisfied with our own contributions need to revitalize our faith occasionally by noting that the summation of modest efforts has contributed quite as much to medical progress as the occasional big discoveries.

However, impressive as the advance has been during the past quarter century, occasions such as this are opportune for reexamining our current methods and procedures with a view to planning still more efficient and economical means for accelerating it. I shall attempt to review the major pathways over which we have reached our present state of progress in medicine, and, as we proceed, shall stop occasionally to note the ruts in the road and obvious suggestions for their repair. Since this assembly is dominantly interested

[1] Address of the vice-president and chairman of the Section on Medical Sciences, American Association for the Advancement of Science, Columbus, December 28, 1939.

in cardiovascular problems, I may perhaps take the liberty of using illustrations in our field; and, as some of the reflections have grown out of personal experiences, I may be permitted to elucidate them by reference to some of my own work. However, the principles have obvious applications to other clinical fields and other laboratory sciences.

A First Pathway of Progress

Some thirty years ago a transition began to occur in the clinical attitude toward disease. Medicine had passed through the empirical, the descriptive, the nosological, the morphological and the bacteriological epochs of development and began to enter the physiological period. By this we mean that interpretation of disease no longer consisted solely in recognizing signs and symptoms, in grouping them into complexes or syndromes and, in the light of past experiences, in giving the disease a name. Rather, disease was regarded as an experiment which nature makes on man and animals, and the clinical objective changed to that of determining what kind of an experiment is going on. In short, the urge developed not merely *to see* but *to see through* the phenomena of disease. ***This change in attitude constituted one important pathway for advance.***

Consider the irregular pulse. As long as clinicians were content to describe and classify irregular hearts and unsuccessfully sought correlations with autopsy findings, the subject remained in a state of chaos. As phrased by Mackenzie, "there seems to be a universal idea in the medical mind that something is very much amiss with the heart that presents an irregular rhythm. As to what that something is no one has any clear idea." As soon as information gained from physiological experiments was logically applied, our understanding of cardiac irregularities and the importance of different types became clearer.

A Second Pathway of Progress

It must not be supposed that this transition involved any abrupt change in the clinical approach toward disease or that no further advances occurred through processes that had dominated previous epochs. There was, and still is, ample opportunity for application of bacteriological and morphological sciences. Important contributions are still made through the processes of observation and description of disease. In fact, nothing can substitute for the power of accurate observation, either at the bedside or in the laboratory. But, during this era, clinicians recognized more definitely that many phenomena of health and disease can not be detected by our unaided senses or, if detectable, can not be adequately analyzed. With this came the greater appreciation that the microscope, the test-tube and—in the case of the heart and circulation—certain instruments developed and tested in physiology laboratories could translate these phenomena into forms that our minds can grasp. Through use of such instruments, our scope of observable phenomena increased tremendously; and, with this greater stock of facts, it became easier to interpret nature's experiments. We need only mention the aids thus gained in studying cardiovascular disease from introduction of pulse recorders, blood pressure apparatus, roentgen rays, electrocardiographs, phonocardiographs, etc. ***The extension of observable phenomena through the use of instrumental laboratory aids therefore constituted a second pathway for advance.***

The clinician has employed these implements well; indeed, by their use he has not merely aided in the understanding of disease, but in many instances has extended our knowledge of physiological processes. However, it should not be overlooked that most of these valuable instruments were designed, tested and continuously improved by physiologists. In many cases, the information obtainable was elucidated by previous laboratory experimentation. I mention these facts, not to garner an unshared credit for physiologists, but to emphasize that a silent process of cooperation and correlation has existed for many decades.

A Third Pathway of Progress

A third pathway for clinical advance was opened when clinicians attempted to reinterpret observations —old and new, direct and indirect—by application of new physiological discoveries. This tendency was marked by the appearance of special texts on applied, clinical and pathological physiology and of monographs on special subjects. In some fields—in electrocardiography, for instance—new physiological discoveries were quickly applied clinically and have reaped a rich reward. Unfortunately, this has not been true in all branches; in far too many, the newer physiology has not been utilized as fully as it might have been. This is true quite generally in the consideration of the dynamics of the circulation, with the result that the dynamic changes concerned in valvular disease, cardiac failure, etc., are still explained in ways that are neither very deep nor very accurate. Too frequently clinicians neglect physiological knowledge altogether and invent various similes to clarify processes for themselves and others. While the adult mind continues to delight in kindergarten pastimes, their substitution for sound thinking in the realm of physics is scarcely in keeping with medical science of the present age.

The reason for the slow absorption and utilization of new physiological discoveries is obvious. Physiological phenomena are abstract; they do not appeal directly to our unaided senses. Generally, they require complicated apparatus and procedures for their elucidation. This involves the continual introduction of

new techniques unfamiliar to the clinician. In order to describe or express facts so discovered, new words, terms and phrases need to be coined; indeed, in some instances, the thoughts are incapable of expression in words and need to be communicated through the medium of mathematics. For this reason, many an interesting discovery of useful knowledge remains in the cocoon stage because ideas can not be expressed in simple language. The slow metamorphosis that modes of expression undergo delays the birth of many physiological discoveries having a practical value.

May I illustrate the dormancy of laboratory discoveries of daily clinical importance in relation to the dynamics of mitral insufficiency—a topic which every competent clinician professes to understand. In 1922, Dr. Feil and I raised a number of interesting questions. Among them were the following: How, with a grossly incompetent mitral valve, can the left ventricle raise the pressure in its cavities with normal speed and to normal heights? What, indeed, prevents all the blood from being expelled from the ventricle into the auricle against a low pressure rather than partly into the aorta against a high pressure. I should be interested in the answer that competent clinicians would give to these questions to-day, *i.e.*, eighteen years after they were elucidated by modern experimental methods. Suffice it to-day if I stimulate your curiosity, but I may say that the physical conditions for minimal regurgitation are contingent upon a forceful ventricular beat; if the heart is extremely hypodynamic all the blood *does* regurgitate into the auricles. Obviously, such a type of research is fundamental in understanding (1) why myocardial insufficiency is of much greater significance in producing circulatory unbalance when the mitral valves are incompetent, and (2) why improvement in ventricular contraction, *e.g.*, that induced by drugs, reduces the percentile regurgitation and thus aids in compensation.

Delayed recognition of important physiological discoveries frequently continues untenable and wrong points of view. I offer a pertinent illustration! The clinician and the pathologist are concerned in explaining the frequent death following coronary thrombosis. The experimental physiologist finds it more difficult to understand why the patient so often lives. The clinician and pathologist invoke the existence of an adequate collateral circulation. This is certainly not the complete answer, for it happens also in normal dogs in which no functional collateral supply of any importance exists and in which Dr. Tennant and I showed that the entire ischemic area fails to contract within about one minute after ligation of a coronary branch. Indeed, after about thirty minutes, this appears to be irreversible.

With deletion of such a large contracting mass, the pressures within the ventricles and aorta may be expected to fall. However, as Dr. Orias and I demonstrated, the remainder of the muscle at once compensates by giving more vigorous contractions, owing to immediate operation of the fundamental laws of initial tension and initial length—first demonstrated for the frog's heart by O. Frank and extended to the dog's heart by Starling. Hence, if the animal or patient is fortunate enough to escape an initial fibrillation or irregularity and the remaining heart muscle is in good physiological condition, the chance for survival is good.

Apparently greater mutual efforts ought to be made by clinicians and physiologists for better dissemination, digestion and absorption of important physiological discoveries. Attendance at each other's meetings, interdepartmental conferences, reciprocal attendance at ward rounds and especially designed laboratory demonstrations serve to stimulate such interest. Real attainment of these ends can come only through individual effort. The physiologist owes a duty to make current knowledge easily available through current abstracts, annual reviews, special monographs and up-to-date text-books of physiology. The clinician must so arrange his life that time is set aside for serious study of such summaries of knowledge. Indeed, time should be as definitely allotted for such perpetual study as it is in every busy life, for music, art, movies, golf, hunting, baseball, etc. In fact, as Dr. Vaughan was accustomed to admonish us, "the busy individual can always find time to do what he wants to do."

A Fourth Pathway of Progress

A fourth pathway for clinical advance, which many regard as the real avenue of progress, was the assumption of active investigation by clinicians themselves. A number of forces motivated clinicians in this new venture:

(1) While clinicians recognized that they were being assisted in the task of interpreting nature's experiments by application of physiological knowledge, this did not satisfy the growing urge to comprehend disease reactions fundamentally. Consequently, efforts were made to hasten an understanding, not only by investigation of patients, but by animal experiments in which clinical conditions were reproduced or simulated.

(2) At the time that such investigations were inaugurated, physiologists generally were concerned chiefly with the orderly solution of fundamental problems regardless of their immediate practical application, and, if interested in disease at all, were so only for the information it gave regarding physiological problems. The clinician, on the contrary, became interested in experimental work for the light it shed

on processes of disease and, being constantly confronted by these problems, naturally designed more pertinent types of experiments.

In 1930, Rufus Cole, in reviewing a quarter century of progress on the occasion of the twenty-fifth anniversary of the Harvey Society, pointed out that the constitution of that society in 1905 contained no provision for inclusion of clinical investigation in its programs; the reason being that no such science existed. During the three decades or more that have passed, clinical investigation has increased by leaps and bounds, so that the clinician without an active experimental laboratory attached to his wards is apt to be called *passé*. Through such activity, clinical medicine has advanced in many directions. New outlooks have been opened, and our range of vision has been extended; with beneficial results in the management and treatment of many diseases. In this forward march of progress, cardiovascular research in hospitals and associated laboratories has been in the front ranks. Consider the field of electrocardiography alone. Einthoven, a physiologist, had contributed not merely by designing the string galvanometer but in showing the uses of electrocardiograms in diagnosis of the simple arrhythmias, hypertrophy of cardiac chambers and changes in position of the heart. The experimental work of Sir Thomas Lewis, his pupils and disciples, extended the work to include curious ventricular beats and many obscure rhythms and sequences of the heart. Since these epoch-making experiments, the pendulum has swung across the Atlantic, and to-day leadership in cardiology rests in our midst. We need only recall the progressive advances in recognition of coronary obstruction by standard leads, the introduction of chest leads, etc. In other fields, such as heart failure, decompensation, hypertension, coronary obstruction, pericardial interference with cardiac action, injury of the heart and peripheral vascular disorders, American leadership stands out conspicuously. We are fortunate that many of the foremost contributors in their fields are with us to participate in our symposia. Under such auspices, it would be presumptive for your chairman to enlarge upon their contributions.

The discipline of science demands, however, that in the same breath that we pay tribute to our successes, we also examine our shortcomings and mistakes. Progress in any field of research is measured less by quantity than by quality of work. Quality is at least a three-dimensional attribute. It involves (1) length, as regards time spent in execution of the work and in its preparation for presentation, (2) breadth, as regards experience and vision in setting the problem, choosing proper and dependable methods, etc., and (3) depth, as regards caution in restricted interpretation of demonstrated facts and understanding in their integration with those previously established.

A perusal of current journals strongly suggests that improvement in quality of research has not kept pace with increase in quantity. Far too much is characterized neither by breadth of vision, depth of understanding nor restraint in generalization unwarranted by the facts. As Cushney phrased it well, "much base coin passes for legal tender."

This criticism applies to investigations emanating from laboratories of clinical as well as fundamental research. Nevertheless, an impartial evaluation of the yearly publications from these two sources reveals, I believe, a greater proportion of immature, uncritical investigation in the clinical field. Others have delicately hinted at such a situation—but no one has attempted to analyze the reasons.

I raise the issue, not with the motive of extolling the superior quality of research in fundamental medical sciences. I raise it with the conviction that, unless we enter the years before us either with greater increased financial support or with greater economy of effort in clinical research, our rate of progress will retard, not accelerate. I raise the issue because I feel that the mutual regard of laboratory and clinical investigators for each other is such that frank, respectful criticism is welcomed, not resented. And I raise the question particularly because the reason seems clear and the prognosis is good.

Let us examine the situation. Those familiar with contributions of clinical investigation will probably agree that the really outstanding ones emanate (1) from departments in which the chief is better known as an investigator than as a diagnostician or therapeutist, or (2) from departments in which the chief, though not necessarily an experimentalist by training, organizes and inspires a group of investigators each with some specialized training. Such a happy combination of a capable clinician and laboratory-trained investigators gives a well-directed impulse to the investigation of disease and assures a reliability in the execution of the experiments. Such alliances ought to be encouraged. However, the plan is costly and, if universally adopted, would strain the supply of investigators trained in laboratories.

The bulk of clinical investigation is carried out in departments which, for lack of large financial support, can not be organized in these ways. In such departments investigative work is either attempted by older men who have achieved eminence in clinical practice or is delegated to younger men who aspire to higher academic posts through the medium of clinical research. Unfortunately, both groups often fail to realize that research requires more than the ability to formulate questions and the zeal to master difficult techniques. They forget that training and practice are fully as important in laboratory experimentation as in bedside diagnosis. They forget the injunction of

Claude Bernard that "we must be brought up in laboratories and live in them to appreciate the full importance of all the details of procedures in investigation which are so often neglected or despised by false men of science calling themselves generalizers."

Let us compare the routes over which most of these young medical men enter research with the approach of those who enter laboratory research *via* a doctorate in philosophy. Two young men, conveniently called Ph.D. and M.D., with approximately equal mentality, ability, and zeal, graduate together from college at the age of 21 years. Both aim to enter experimental fields but choose different approaches. Upon attainment of their respective doctorates at 25, Ph.D. has had about two years of research apprenticeship to his credit; M.D., of course, has had none. Ph.D. obtains an academic post and, if alert and wise, will find means to continue investigation for the next two years. During these times opportunity arises for displaying his initiative and inventiveness, but the methods he employs, the interpretation of results and particularly their publication still require guidance. The medical graduate, still with the urge to pursue a research career, might of course also enter a laboratory field, as was considered good and even noble practice in my day. But wisely or unwisely, this is no longer considered quite regular and in some states, unlawful. At any event, usually upon advice of his clinical professors, he elects to complete two intern years, during which he is exposed to no investigative work. Thus at 27 years, Ph.D. is already well launched upon a research career, whereas M.D. has not even started. M.D. realizes that he must either attain research equivalence four years later than his laboratory friend or adopt some short-circuit method. If he chooses the latter—and he too generally does—the danger begins. With the misguided concept that acquisition of laboratory technique and research procedure are easily acquired, he plunges into the turbulent waters of clinical investigation. Generally he is left to his own resources, on the theory that one learns best through experience. Guidance and training in precision of execution, caution in continually mistrusting apparent answers yielded by experimentation are generally wanting. Through industry and zeal, results and conclusions are forthcoming. These appear of mountainous significance to him. They are published and praised in local circles; they may be quoted and requoted in uncritical reviews, and he is acclaimed an investigator of promise. But a critical perusal of his work will generally reveal the inadequacy of training and immaturity of judgment of which I have spoken. He fails to realize that, while experiments generally give answers to questions asked, they do not always yield the correct ones. Now it may fairly be asked how an individual with two years of unguided research can hope to compete with another having six years of guided experience. This is the status of M.D. and Ph.D., both engaged in research, at the age of 29 years. This inequality of opportunity to gain experience in experimentation and the venture to short-cut the training is responsible for the mediocrity of much clinical research. Given equal mentality, ambition and zeal, the clinical investigator is at a serious disadvantage. Not infrequently he realizes the situation, and, with the mounting family and social obligations that inevitably enter, he abandons research to enter the practice of medicine. True, his experience is not lost; he is the better practitioner in consequence. But he is lost to clinical research at the beginning of an investigative career, and the results of his immature publications remain forever to confuse the literature.

A number of plans could be devised by which greater equality of opportunity could be achieved. I offer one suggestion that seems to have worked in some instances. The scheme involves encouragement of a few medical students with inclinations for an investigative career to break their medical course at the end of the second year and to assume a fellowship in an experimental laboratory. This should carry a stipend sufficient to defray the cost of the extra year. The work should be so organized that the student gains a year's apprenticeship in laboratory research. After completing his medical studies, a two-year medical internship should be reserved, in which provision is made for participation in a well-organized clinical or laboratory investigation for half of the time. If then he continues in a clinical post which offers ample time for research for another two years, he would, at the age of 29 years, have gained four years of research training and be well launched to undertake independent investigation.

Other plans, of course, are satisfactory. For example, many young doctors after completion of their regular intern years find it feasible, despite the pursuing years, to return to laboratories of fundamental science for methodical training in research. Those of us who direct such departments should make every effort to assist these earnest men. I have made it a practice for some years to keep two salaried places on my staff on a rotational basis for the purpose of training suitable candidates of this type. The results have proved mutually beneficial. But many years the number of applicants exceeds the places available. Foundations desirous of aiding clinical research by starting young men properly in such careers are unable to help all that are worthy of such assistance. More fellowships for the explicit purpose of training promising medical men in the *technique of research* are still urgently needed. In experimental physiology these fellowships should be for a period of two years,

since this is the minimal time in which an adequate training can be acquired.

A Fifth Pathway of Progress

In our discussion, it has become apparent that physiology has contributed in various supplementary ways to the success of clinical progress, and several other ways in which it could be of further service have been indicated. What other rôles can experimental physiologists as a class properly play in accelerating the advance of medical science. Physiologists as individuals will probably give different answers. A considerable group still hold, as one current textbook states in the preface, that "the greatest service which physiology can render modern medicine is to continue to solve fundamental problems which are not necessarily of immediate practical concern." Another group, of which I am one, believes that, while the orderly solution of fundamental problems should remain a dominant aim, physiology and clinical medicine are aided simultaneously by researches of a more practical sort carried out by physiologists.

It happens frequently, certainly in cardiovascular research, that data and observations gained through clinical studies need to be referred back to laboratories of physiology, because the fundamental premises involved in their interpretation are not sufficiently understood. All too often, clinical research is not concluded until such additional knowledge is available. May I illustrate by a reference that falls within my field of experience? It concerns the dynamics of aortic insufficiency. Sound physiological teaching has assigned to the aortic valves the function of preventing backflow into the ventricle during diastole. Clinicians therefore arrived at the *a priori* conclusion that a large backflow of blood must necessarily occur when these valves become incompetent. Now, ever since Corrigan in 1832 described the typical peripheral pulse of aortic insufficiency which bears his name, the rapid collapse was attributed to such diastolic regurgitation. In 1908, clinical investigations on patients brought forward a serious difficulty, *viz.*, that the rapid drop in radial sphygmograms precedes the dicrotic wave and therefore seems to come during systole. Supplementary experiments on animals *by clinicians* then apparently demonstrated (1) that the volume of regurgitation is apparently not large, and (2) that the collapse of the pulse is due to reflex vasodilation which simultaneously explains the capillary pulse. In 1914, I restudied the question experimentally by more advanced methods. It was found (1) that a similar collapse occurs during aortic insufficiency in an artificial circulation machine when the peripheral resistance is *not* altered, (2) that in dogs the characteristic changes in the pulse occur in the first beat after production of a lesion and therefore must be of central origin, and (3) that the collapse is partly systolic and partly diastolic in time, shifting more toward the systolic side, the larger the leak becomes. The cause of the systolic collapse remained an enigma for many years because certain fundamental reactions of the heart were not understood. By continued study of the problem in a physiological atmosphere, it gradually became clear that the overloaded ventricle contracting against a low aortic resistance empties fairly completely during the first half of systole and ejects little blood during the latter half. The peripheral escape of blood from the central elastic reservoir is responsible for the systolic collapse.

Experimental physiologists should continue to participate in the solution of practical questions because their background often enables them to see problems which are not obvious to clinicians. May I illustrate my thoughts with reference to the dynamics of hypertension, a subject to which clinical investigators have contributed in large measure? Physiological research had rather firmly established that an elevation of blood pressure may be due to increases in heart rate, in systolic discharge, in peripheral resistance or in viscosity. Clinical investigations on hypertensive patients excluded all these factors except peripheral resistance; hence, by elimination, the conclusion was drawn that the fault lies in the peripheral arterioles. No one, however, has submitted visual, photographic or other direct proof of the occurrence of such narrowing, except in the retinal vessels. In 1938, I pointed out, using published clinical data, that even the magnitude of the increase in resistance can be gauged by applying hemodynamic formulae. However, the magnitude of the increase did not correspond to the elevation of pressure in different patients. Furthermore, the relative increase in systolic and diastolic pressures found in clinical and experimental hypertension are not those anticipated, either on dynamic principles or experiments from increase in peripheral resistance alone. The suggestion both by clinical investigators and physiologists that an aortic factor must be concerned led to further experiments in which Dr. Wegria and I showed that acute hypertension produced in dogs by humoral or nervous constriction of blood vessels is accompanied by alteration both in the size and elasticity of the aorta. Thus the hint was relayed back to the clinicians that changes in aortic elasticity, previously suspected to occur in hypertension, need not necessarily be demonstrable as histological or elastic changes of the aorta obtained post mortem, but may represent a reactive functional state during life only.

It seems to me that such shuttling of problems between clinical and laboratory investigators, each in turn attacking problems from his respective point of view, offers one of our greatest hopes for understanding the ultimate mechanisms that produce disease.

A SIXTH PATHWAY OF PROGRESS

Finally, the physiologist can frequently link his talents with those of a clinical investigator in the pursuit of collaborative research. Such interdepartmental research is particularly valuable when investigators have interests in similar problems but possess different talents required in their solution. Obvious benefits accrue from such cooperative efforts in the science of research as in the science of warfare. It is important that a feeling of mutual understanding and fellowship exist and, above all, that both parties be ready to disregard self and self-interest. The individual must be subservient to the progress of the research.

Such interdepartmental investigation must necessarily be so ordered that the primary duties of each participant to his own calling do not suffer. Each must be careful to limit his interest. For example, the physiologist who becomes so enamored of clinical problems that he neglects his interest in orderly fundamental studies may be popular with clinicians but soon loses standing among his colleagues.

Older physiologists should ever be ready to assist younger clinical investigators in technical methods, new ways of approach and, if competent to do so, even in suggesting new lines of investigation. Having started a line of investigation and assisted the clinical investigator in the technique of special methods, the physiologist should gracefully withdraw, leaving the field to his clinical associate. In this way, his time becomes free again for other duties or for helping others, but, what is more important, the clinical investigator left with a method as well as a problem is given an opportunity to test his own ability and develop his resourcefulness.

SUMMARY

During the three decades that have passed, medical science has ascended to a high plateau of achievement. The climb has involved several pathways; among them: (1) the physiological approach toward disease as experiments which nature performs on organisms, (2) the more intelligent interpretation of the functional reactions of the body in disease in accordance with latest discoveries in physiology, (3) the supplementation of observable phenomena through use of laboratory instruments, (4) the assumption of active investigation both on patients and experimental animals by clinicians themselves, (5) the shuttling of problems between clinical and experimental laboratories and (6) correlated research in clinical and physiological departments.

As we look down from the heights we have reached, we have reason to be pleased with our progress; but when we look ahead we become aware that there are still high mountain ranges to be climbed. We realize that their ascent can not be accomplished by employing merely the methods, equipment and strategy that have proved successful so far; we must improve the application of principles that are old and well established, and evolve others that are new. Above all, we from laboratories and clinics must join hands to help each other climb; and through correlated teamwork overcome the great obstacles that jealous nature places in our way.

I have ventured to suggest a few directions which such mutual help may take. They include (1) means by which new fundamental discoveries can be utilized more quickly by clinicians and practitioners of medicine; (2) plans by which younger clinical investigators can be given approximately the same opportunity for training in research technique as their colleagues entering experimental sciences; (3) pleas that the shuttling of problems between hospitals and laboratories of fundamental science may continue in order that the ultimate significance of clinical results may be better understood and that the applicability of fundamental discoveries to nature's experiments may be tested; (4) judicious combination of talents of laboratory and clinical workers, whenever this leads to greater economy of effort and does not infringe upon the primary duties of each participant to his calling.

The spirit of correlation which is involved in all these plans of advance is a silent force which grows not only through mutual interest in each other's problems but also through frank respectful criticism of each other's trends. With such a spirit of correlated effort science marches on.

THE SYNTHESIS OF VITAMIN K_1[1]

By Dr. LOUIS F. FIESER

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I HAVE a story to tell to-night about the naming of a cat. This was by no means a simple matter, for it involved a fully pedigreed Siamese aristocrat requiring an appropriate and dignified name. Fortunately, it took all summer to conclude the various arrangements involved in getting the cat born, for this gave time for deliberation on a suitable name for the prospective offspring of Oriental Nanki Pooh and his dam

[1] From an address before the Boylston Chemical Club, Harvard University, October 24, 1939.

Sola Bella Maria. It thus happened that by the time the kitten arrived an incident had occurred providing the inspiration for a baptismal name. In the registry our cat will be known as Sin Kai Pooh, and all that remains to the story is to explain that Sin is our attempted pseudo-Siamese equivalent of synthetic and that Kai stands for a new addition to the list of vitamins now available in a pure form for use in medicine.

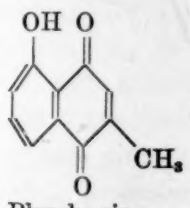
It should be made clear that the discovery of vitamin K and its biological characterization and isolation from natural sources was all the work of others. The brief excursion into the field undertaken during the past summer in our laboratory was of a purely chemical nature and consisted in an investigation of the problem by the methods of synthetic organic chemistry. Guided by an early conception of the probable nature of the vitamin, our work culminated in the establishment of the structure by a synthesis which was accomplished before other evidence was at hand and which has the merit of providing a practical method for the production of the pure material in quantity.

The discovery of the antihemorrhagic principle is due to Henrik Dam, Copenhagen. In 1929 this investigator recognized the occurrence in chicks of a disease characterized by hemorrhages and other pathological changes and by a prolonged clotting time of the blood. Dam established that the hemorrhagic syndrome is due to a dietary deficiency and in 1935 discovered that the preventive factor normally derived from foods is a fat-soluble substance, the "Koagulations-Vitamin." The conclusion was confirmed in independent work by H. J. Almquist and E. L. R. Stokstadt at the University of California. Early tests revealing the presence of vitamin K in various foods were conducted by an approximate preventive method, and Dam's collaborator, F. Schønheyder, later developed a more convenient and accurate curative method (1936). With a satisfactory method of bio-assay available it was soon ascertained that green plants are particularly rich in the vitamin and that dried alfalfa constitutes a suitable source. The initiation of active work on the chemical characterization and isolation of vitamin K was announced independently by Dam and Almquist in May, 1936, both groups reporting the preparation of concentrates by extraction with hydrocarbon solvents and enrichment by adsorption and distillation procedures. In September the problem of isolation was taken up by the research group of E. A. Doisy in St. Louis. The concentration of petroleum ether extracts of alfalfa without destruction of the vitamin proved a difficult task, for the active factor is a delicate substance highly sensitive to alkalis, light and excessive heat, and progress during the three years following the fundamental discoveries of Dam and of Almquist was slow and uncertain. Crystalline preparations believed to be the vitamin or a derivative isolated in this period by Almquist (1937, 1939) and by Doisy (1938) were later recognized as inactive companion substances or reagents.

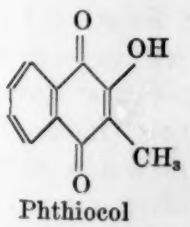
Dam, in attacking the chemical problem, enlisted the cooperation of P. Karrer, Zurich, and in March, 1939, these investigators and their associates announced the isolation from alfalfa of a yellow oil of very high antihemorrhagic activity which they regarded as pure or nearly pure vitamin K. It was difficult to be sure of the absolute purity of the preparation because it was an oil from which no crystalline derivative was obtained, and the authors reserved judgment on this point. They did characterize the substance by bio-assays, by an analysis, by the observation that it gives a beautiful transient purple-blue color with alcoholic alkali and by determination of the ultra-violet absorption spectrum. The absorption curve is of so elaborate a design that it provides an intimate characterization of the vitamin whereby it can be distinguished easily from substances of other types. In May the Doisy group reported the isolation from alfalfa of a similar active yellow oil. Their analytical characterization was more extensive than in the previous work, and a strong case for the purity of the preparation was at hand in the demonstration of a similarity to a second antihemorrhagic factor obtained from putrefied fish meal. While the alfalfa principle (vitamin K_1) is an oil at room temperature, the second substance (K_2) is a crystalline solid, and by determination of the melting point of samples treated in various ways it was possible to secure substantial evidence of purity. Doisy's vitamin K_1 preparation corresponded closely in absorption spectrum with that of Dam and Karrer, except for a displacement of the curve to a region of greater intensity. The intensity of absorption as measured by the extinction coefficient is an accurate index of the relative purity of different samples. Whereas Dam and Karrer had found the coefficient 280 for their preparation, the Americans observed the value 385 and concluded that the previously isolated sample had been only about 70 per cent. pure. They later (June) provided further evidence of the purity of their sample by the preparation of a crystalline diacetate derivative from which material of the original biological potency could be regenerated, and on this occasion they stated that a redetermination of the extinction coefficient had given the still higher value 540. In two further papers Karrer has affirmed the purity of the first preparation but has presented no data in explanation of the discrepancy. Repeated spectrographic determinations on both natural and synthetic samples prepared at Harvard confirm Doisy's first reported extinction coefficient but not the higher value.

In the May report the Doisy group interpreted their analytical results in terms of the formulas $C_{32}H_{46-48}O_2$ for K_1 and $C_{40}H_{54-56}O_2$ for K_2, but of course with

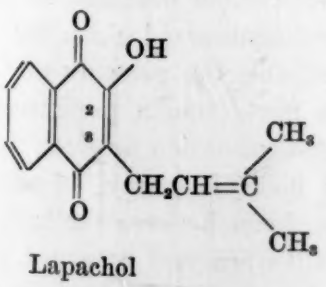
substances of such complexity formulas differing by the increment CH_2 can not be distinguished by ordinary analysis. Of particular moment was the suggestion that the vitamins are quinones, a conclusion based upon the evidence that they both contain two atoms of oxygen and upon the lability and the spectra of the substances and their behavior on hydrogenation. This recognition of the quinone character of the antihemorrhagic factors was of particular interest to me because of an association with the chemistry of quinones dating from work for the doctorate initiated in 1921 under Professor James B. Conant. A research on oxidation-reduction potentials was extended in later years to include a study of some 167 compounds of this special series. Several researches had been concerned with quinones of the naphthalene series, including certain naturally occurring substances. Among the yellow pigments known to be naphthoquinones are lawsone, the yellow dye of henna leaves, juglone, which occurs in the reduced form in walnut shells, plumbagin, a pigment of the Indian drug Chita, phthiocol, isolated from human tubercular bacilli, lapachol, from the grain of certain tropical woods and the related pigments lomatiol, alkannin and shikonin. The structures of a few of these substances are shown in the formulas; that of lapachol is particularly interesting because of the presence at position 3 of an unsaturated side chain with



Plumbagin



Phthiocol



Lapachol

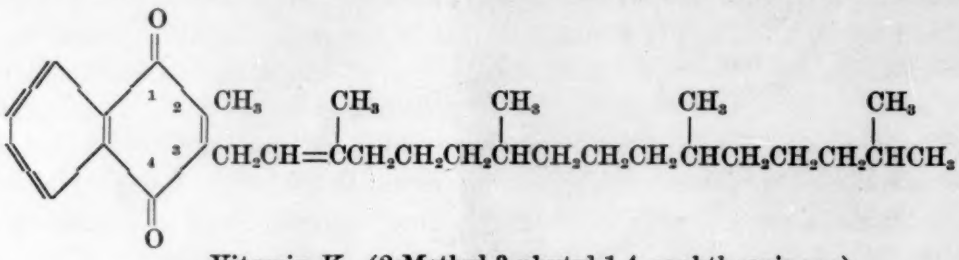
the grouping $C \cdot C \cdot C\ (C)_2$ characteristic of isoprene and of isoprenoid substances such as the terpenes, rubber and vitamin A. Following an extended study of lawsone, interest in lapachol had led to an immensely gratifying association with the late Samuel C. Hooker, whose remarkable investigations in the lapachol field are a classic of masterly experimentation. An outcome of this inspiring contact was the synthesis of lapachol and later (with J. T. Dunn) of plumbagin.

When the vitamin K problem emerged from chemical obscurity into a field actively explored in our laboratory for some eighteen years, we considered at once ways in which the accumulated experience, information and supplies could be employed in advancing the problem. Doisy had found that vitamins K_1 and K_2 correspond closely in spectrum and they therefore must be of the same structural type. Since they both possess antihemorrhagic activity, even though they differ considerably in composition, it occurred to us that simpler quinones of the proper general molecular pattern might show vitamin K activity. It was also apparent that the distinctive absorption spectra of the vitamins should provide an excellent guide for discovering the type of quinone required. The behavior on hydrogenation noted by Doisy was reminiscent of my past experiences with lapachol and suggested the presence of an unsaturated side chain. Since the allyl group ($—CH_2CH=CH_2$) is the simplest such chain which can be introduced by synthetic operations, we undertook to synthesize certain allyl quinones of the benzene and naphthalene series.

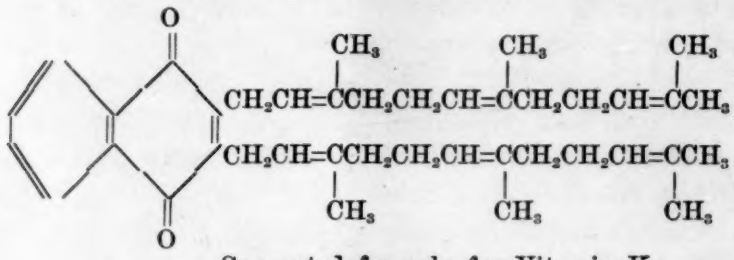
Our experiments were started on May 18, arrangements having been made for assays in the Merck laboratories. On the nineteenth Dr. R. N. Jones, who had surveyed the literature for pertinent spectrographic data, presented an array of comparisons which indicated that the vitamins are α-naphthoquinones. The vitamin factors are characterized by intense bands centering at 246 and 265.5 mμ and a broad band of low intensity at about 322 mμ, and among quinones previously investigated such a spectrum had been encountered only in the α-naphthoquinone series. Dr. Jones noted that the parent quinone and its 2-methyl derivative correspond only roughly, for they lack one of the two intense bands, but that 2,3-diacetoxy-1,4-naphthoquinone has a spectrum strikingly similar to that of the vitamins, the measurements of Macbeth, Winzor and Price (1935) indicating intense maxima, a 246 and 265 mμ and a broad band at 330 mμ. It seemed probable from this comparison that the vitamins are 1,4-naphthoquinones with alkyl substituents at the 2 and 3 positions, and the presence of such blocking substituents would account for an inertness to certain reagents noted by Almquist. Confirmation was provided a few days later in a letter from Dr. Byron Riegel, Northwestern University, who had found that the oxidation-reduction potential of vitamin K_1 is about that expected for a 2,3-dialkyl compound and who independently had conceived the idea of testing simpler substances of this type.

With this concrete basis for speculation, it occurred to us on the twenty-third that all the known facts could be explained on the hypothesis that vitamin K_1 is

2-methyl-3-phytyl-1,4-naphthoquinone, or a methyl homologue, and that vitamin K_2 is 2,3-difarnesyl-1,4-naphthoquinone (see formulas). Of prime importance



Vitamin K_1 (2-Methyl-3-phytyl-1,4-naphthoquinone)



Suggested formula for Vitamin K_2

was the belief that the vitamins are derived by a simple process of biogenesis from building units of recognized natural types. A naphthoquinone nucleus seemed clearly indicated, as with the known yellow pigments mentioned above, and analogy to lapachol suggested the presence of unsaturated isoprenoid side chains. From a somewhat daring interpretation of Doisy's hydrogenation results it was inferred that in these side chains vitamins K_1 and K_2 have one and six double bonds, respectively. The problem then resolved itself into picking isoprenoid alkyl groups having the proper carbon content, degree of unsaturation and composition, and inspection of the following list of known isoprenoid alcohols will show that there was little choice: citronellol ($C_{10}H_{19}OH$, 1 C:C), geraniol ($C_{10}H_{17}OH$, 2 C:C), farnesol ($C_{15}H_{25}OH$, 3 C:C), phytol ($C_{20}H_{39}OH$, 1 C:C), vitamin A ($C_{20}H_{29}OH$, 5 C:C). The alfalfa principle was known to contain approximately 21 carbon atoms in addition to those of the naphthoquinone unit. If two C_{10}-groups or one vitamin A residue were assumed as supplying the remaining carbon complement the unsaturation would be greater than that required. A phytyl and a methyl group, however, would give not only the right carbon content and composition, but exactly the degree of unsaturation noted. The fish meal principle must have a total of approximately 30 carbon atoms and 6 double bonds in the side chains, and both requirements, together with the composition, are accurately met by the assumption of the presence of two farnesyl groups, and again there is no alternative. From certain observations of Hooker it could be inferred that the yellow substance has no double bond adjacent to the quinone ring, and the absence of characteristics in the spectrum associated with the system C=C—C=C showed that the double bonds are not adjacent to one another. The symmetrical farnesyl pattern provides a rational distribution admissible on both scores, and indeed it can hardly be a coincidence that only one known alcohol meets all these exacting requirements.

The idea seemed all the more attractive from the evident analogy to vitamin E, a condensation product of phytol with a hydroquinone of the benzene series. It seemed reasonable that the vitamin occurring in green leaves should be the one derived from phytol, for phytol is a constituent of the green leaf pigment chlorophyll. Furthermore, the farnesyl group postulated as present in the fish meal principle is the building unit of the hydrocarbon squalene, which occurs in certain fish oils.

Analogy in support of the structures was soon forthcoming in the observation that the simple model compound 2,3-dimethyl-1,4-naphthoquinone has the vitamin K type of spectrum and possesses definite antihemorrhagic activity. With this favorable indication, a joint communication with Dr. Riegel and his associates was presented on June 12 setting forth the above theory. This was the first suggestion of specific structures and the only one concerning vitamin K_2 which has yet appeared. On the appearance of the July *Journal* we learn that a week after our report Doisy and co-workers had presented degradative evidence establishing the naphthoquinonoid character of vitamin K_1 and making probable the presence of the phytyl group. Arguing in part from a preliminary characterization of a certain degradation product, they suggested the structure of 2-ethyl-3-phytyl-1,4-naphthoquinone. We felt that a choice between the methyl and ethyl structures was still open and regarded the former as the more likely because of the analogy to plumbagin and phthiocol.

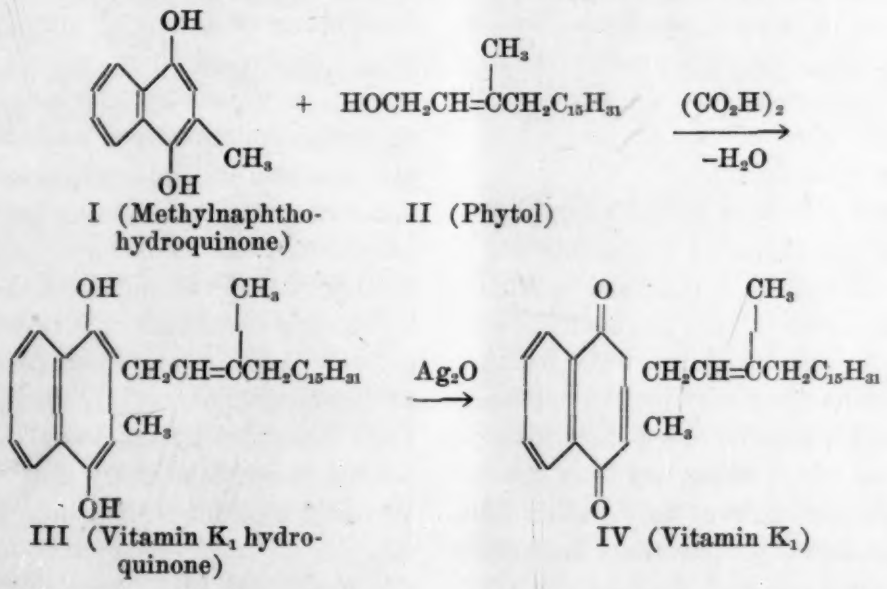
By the end of June we had observed that the allyl-naphthoquinones synthesized as possible models exhibited the color phenomenon stated in Karrer's laboratory to be characteristic of vitamins K_1 and K_2, and the reaction was recognized as an indication of the presence of a β-unsaturated side chain as postu-

lated. Certain of the models also showed detailed features of the complex vitamin K spectrum. All efforts were then directed toward the synthesis of 2-methyl-3-phytyl-1,4-naphthoquinone. We considered and briefly tried various rather elaborate schemes but always came back to the idea that there must be some simple way of causing phytol to condense directly with methylnaphthoquinone in either the oxidized or reduced form, for this seemed the obvious course of the biosynthesis. Good use was made of model compounds in exploring possible reactions, for the simpler products are more easily identified. It was found that methylnaphthohydroquinone is better suited to the reaction than the quinone, that alkaline condensation can be employed successfully but gives dark products in poor yields, and that mineral acids are too destructive and carry the condensation too far, giving products of the vitamin E rather than K type. A milder acidic reagent seemed called for, and we eventually found that the desired reaction can be brought about using oxalic acid in dioxane solution.

The condensation of phytol with methylnaphthohydroquinone apparently proceeded in the right direction to give some of the desired product III, but this was evidently mixed with by-products of similar properties and with unchanged starting materials. It appeared at first that the separation of the product either as such or as the quinone would be about as difficult as the isolation of vitamin K_1 from alfalfa concentrates by existing methods, and this is indeed the case if oxidation by the air is not prevented by suitable use of sodium hydrosulfite. By keeping the materials in the reduced condition the isolation is accomplished in an extremely simple and efficient way. By extraction with dilute alkali the starting hydroquinone I is separated completely from the weakly acidic phytyl-substituted hydroxy compounds, and on treating the residual dark oil with petroleum ether the desired hydroquinone III separates as a white solid and all the impurities and by-products pass into solution. The white solid is collected and washed by centrifugation, and oxidation with silver oxide gives the quinone IV as a light yellow oil in a directly pure condition. The whole operation is easy and the yield good.

This synthesis of 2-methyl-3-phytyl-1,4-naphthoquinone was completed on August 1, and it was at once apparent from a positive color test that it was of the vitamin K type. Within a few days the synthetic quinone was found to give the expected analysis, the absorption spectrum corresponded precisely in every detail with that of the natural vitamin, and in the chick assay the antihemorrhagic activity was comparable with that of the alfalfa principle. The hydroquinone diacetate, prepared for comparison with the crystalline derivative described by Doisy, was obtained as an oil which eventually crystallized in colorless needles having the correct analysis and melting point. This evidence was all complete on August 10, and, after ascertaining that a mixed melting point comparison could not be obtained without some delay, the results were communicated on the twelfth.

The exact correspondence in color reaction, analysis, spectrum, assay and melting point of the diacetate provided a strong indication of identity but not a complete proof. If the vitamin were the ethyl compound as postulated by Doisy one would anticipate correspondence on the first three points and possibly on the fourth. From observations with model compounds we could say that the agreement in melting point of the diacetates probably ruled out the ethyl structure, but probability is not proof. A mixed melting point determination was desirable, even though with fatty substances the absence of a depression may not be an absolute guarantee of identity. Pure natural vitamin K_1 was required for the direct comparison, and it occurred to us that the isolation might be accomplished more easily than heretofore by processing the material in the reduced form by the method found



so convenient in working up the synthetic reaction mixtures. It soon developed that a good way to discover how best to isolate a vitamin is first to synthesize it! A small sample (5.3 g) of 3 to 5 per cent. alfalfa concentrate kindly supplied by Dr. Riegel was reduced and put through extraction and precipitation procedures worked out with the synthetic substance, and in a few hours' working time 60 mg of pure vitamin K_1 was isolated. This sufficed for analysis, color test, assay, determination of the spectrum and for the preparation and analysis of the crystalline diacetate. In every instance direct comparison of the synthetic and natural substances indicated exact correspondence, and there was no depression in the mixed melting point determination. Finally, 2-ethyl-3-phytyl-1,4-naphthoquinone was synthesized and found devoid of vitamin K activity, an observation which effectively disposed of the only alternate possibility. We were thus in a position on August 25 to state positively that vitamin K_1 is identical with our synthetic product and has the structure of 2-methyl-3-phytyl-1,4-naphthoquinone. The structure had been fully established in a program of synthetic research independent of any work on the vitamin itself.

The provisional evidence of Doisy and co-workers pointing to the presence of an ethyl group was found by these investigators to have been in error, and in a communication of August 21 they reported completion of degradative experiments which provided full proof of the structure defined above. They thus announced the structure ahead of us, for we were not able to provide the completing evidence of the mixed melting point determination until a few days later. The St. Louis workers reported a second synthesis, by an alkaline method of condensation, of a product isolated as the hydroquinone diacetate, and on the twenty-fifth they recorded ample evidence of the identity of this derivative with that of vitamin K_1.

The elucidation of the structure of the vitamin was one important goal of the chemical investigations; a second was the development of a practical synthesis suitable for the manufacture of the pure vitamin in such quantity as may be required in medical practice. The objective seems to be fully met by the synthesis devised at Harvard, and it may be noted that this first synthesis is the only one which as yet has been demonstrated to afford the pure vitamin as such, rather than as a derivative. Trial batch preparations have been carried out in a commercial laboratory giving in a short working period quantities of vitamin equivalent to as much as 30,000 pounds of dried alfalfa. The synthetic material has been found completely innocuous in toxicity tests and has given excellent results in clinical trials.

The testing of simple quinones for antihemorrhagic activity has been conducted in several laboratories in this country and abroad, and Almquist was the first to discover activity in such a substance (phthiocol). Particularly striking is the discovery of S. Ansbacher and E. Fernholz that methylnaphthoquinone is three or four times as potent in the chick assay as vitamin K_1, and it is possible that this available and inexpensive substance may find use in therapy as a substitute for the natural principle. There are reasons for reserving judgment, however, for although the compound apparently is quite safe for administration in small doses and has shown high potency in numerous chick assays it does have a certain toxicity and irritating action on the skin not found in the vitamin, and the results in the early assays were so irregular as to lead three research groups to regard the substance as at most feebly active. The high sensitivity and chemical reactivity of the quinone may present an interfering factor, and if an inexpensive substitute is required it might be preferable to employ a substance more closely related to the vitamin, for example, 2-methyl-3-geranyl-1,4-naphthoquinone. Water-soluble derivatives may ultimately prove of particular value, and a series of hydroquinone esters having this property has been prepared in our laboratory.

Much remains to be learned concerning the origin, functioning and fate of antihemorrhagic compounds. The paradoxical high potency of methylnaphthoquinone may possibly be accounted for on the hypothesis that the administered material becomes reduced and provides one of two components required for a synthesis of vitamin K in the organism paralleling that achieved in the laboratory. Another interesting possibility is that the phthiocol isolated from tubercular bacilli after alkaline hydrolysis was not originally present as such but arose as a degradation product of the antihemorrhagic principle shown by Almquist to be produced by the bacteria. At least it has been proved in our laboratory that vitamin K_1 can be converted into phthiocol by gentle treatment with alcoholic alkali.

OBITUARY

JONAS BERNARD NATHANSON

ON November 25 death came without warning to Jonas Bernard Nathanson, of the Carnegie Institute of Technology. He collapsed while preparing to attend the theater with his family, and death came shortly after the arrival of the physician. Thus "An able teacher, an accomplished scholar, an earnest seeker after truth, a good and loyal friend is gone from our midst."

Jonas Bernard Nathanson was born on November 5, 1889, in Vilna, Lithuania. He came to this country when quite young and received his early education in

the schools of Toledo, Ohio, where his family resided. He attended Ohio State University and received his A.B. degree in 1912. He then attended the University of Illinois and received his A.M. degree in 1913 and his Ph.D. degree in 1916. He was assistant in physics at the University of Illinois from 1913 to 1916. He was an instructor in physics at the Carnegie Institute of Technology from 1916 to 1919; assistant professor of physics from 1919 to 1930; and associate professor of physics from 1930 until his death.

While at the University of Illinois he became interested in the optical properties of the alkali metals. This interest continued during the remainder of his career, and he contributed many papers in the field, also researches on the ratio of the charge to the mass of the electron interference in metallic films and optical dispersion of metals.

He was a member of Phi Beta Kappa, Sigma Xi, Phi Lambda Upsilon, American Association for the Advancement of Science, American Physical Society, Optical Society of America, Physical Society of Pittsburgh (president, 1929), American Association of Physics Teachers and the Association of Physics Teachers of Western Pennsylvania and Environs.

Dr. Nathanson's interest in research continued to the end. He inspired and assisted many students in numerous investigations. He was invited to talk before many scientific societies on his chosen research. His keen insight, thorough understanding and unselfish interest contributed to his success as a teacher. His clear and accurate presentation created in the student an orderly and thorough method of thinking. "He will long be remembered for his enthusiasm, frankness, sincerity, patience and modesty."

He is survived by his widow, Rose M. Nathanson, and one daughter, Carol E.

CHAS. W. PRINE
CARNEGIE INSTITUTE OF TECHNOLOGY

IN HONOR OF GEORGE FREDERICK ARPS

IN memory of the late George Frederick Arps, who died a year ago, the educational building of the Ohio State University has been renamed Arps Hall. Dr. Arps joined the faculty of the university as assistant professor in 1910, becoming professor of psychology in 1912. He was known for his work on experimental psychology on attention, visual discrimination and color induction. Dr. J. L. Morrill, vice-president of the university, prepared the following tribute, which has been adopted by the board:

The Board of Trustees learns with deepest sorrow of the death of Dr. George F. Arps, professor of psychology since 1912; Dean of the College of Education, 1920 to 1937; and Dean of the Graduate School since May, 1937.

A teacher with the gift of contagious enthusiasm for learning, a scholar of distinguished training and attainments, an administrator of rare vision and unusual accomplishment, a counselor and companion whose generous comradeship was cherished by his colleagues, Dean Arps exemplified in his life and work the highest ideals of effective and enduring service to the Ohio State University. A distinguished figure in the world of higher education in America, by his own leadership and by the contributions to teaching and research of those whom he encouraged, assisted and inspired, Dean Arps conferred honor and prestige upon the institution which he served with unremitting labor and devotion. In his passing the university suffers irreparable loss.

Be it therefore resolved, that the Board of Trustees hereby expresses on behalf of the university its appreciation of a great spirit committed to high service, a character whose memory will remain as a challenge to constructive accomplishments, and

Be it further resolved, that in his memory the present Education Building on the campus with which he was so long and conspicuously identified be designated from and after this date as "Arps Hall"; and further that a copy of this resolution be spread upon the minutes of the board and transmitted to the members of the family with the sympathy of the board and of the university.

RECENT DEATHS

PROFESSOR JACOB E. METZGER, director of the Experiment Station, professor of agronomy and head of the department at the University of Maryland, died on December 25, 1939, at the age of fifty-seven years.

DR. HENRY LESLIE OSBORN, professor of biology and geology and dean emeritus of Hamline University, St. Paul, Minn., died on January 3. He was eighty-two years old.

CHARLES NICOLAS AINSLIE, entomologist in the United States Department of Agriculture, 1906–1930, and collaborator thereafter, died on December 5, 1939, at the age of eighty-three years.

DR. ALMON ERNEST PARKINS, professor of geography at the George Peabody College for Teachers at Nashville, Tenn., died on January 3 at the age of sixty years.

DR. GEORGE CHARLTON MATSON, consulting geologist and an independent oil operator of Tulsa, Okla., formerly geologist of the U. S. Geological Survey, died on January 3 in his sixty-sixth year.

SCIENTIFIC EVENTS

THE NEW FEDERAL NUTRITIONS LABORATORY AT CORNELL UNIVERSITY

A COMPREHENSIVE research project on the nutritional values of foodstuffs will be undertaken at Cornell University during the summer.

An appropriation from Bankhead-Jones funds has been made available for three laboratories and greenhouses at the university, in which the U. S. Department of Agriculture will center investigations extending throughout the United States. The second unit of

the new federal nutritions laboratory at the university is now under construction. Professor L. A. Maynard, head of the department of animal nutrition at the university, has been appointed director of the laboratory. He will work in conjunction with Dr. E. C. Auchter, chief of the Federal Bureau of Plant Industry.

Nearly all the efforts of the past have been directed toward increasing the production of foods. A serious attempt will now be made to increase the nutritional value of foodstuffs through studies of soil and crop management, soil types and plant and animal nutrition.

Commenting on the program Secretary Wallace said:

> Work at the new laboratory is expected to develop facts that will enable practises in soil management and crop production to be dovetailed more closely with human nutritional needs. Agricultural scientists have done a good job in solving problems of quantity production and market quality. To-day, new advances in the science of nutrition make it necessary to think about doing an equally good job on quality production as it relates to nutritional value.

One of the early steps will be a survey of mineral resources in the soils of the United States—not the minerals that are used as precious metals or industrial materials—but the vital elements that must be obtained from foods, which in turn get them from the soil.

The official announcement points out that

> soil deficiencies often show up in plant life. In turn, animals feeding on these plants develop deficiencies which seriously affect their health. A striking case is that of animals in certain areas which waste away and die because of a lack of cobalt in the soil and forage. The animal's daily need of this mineral could be held on the head of a pin. One of the objectives of the research program is to determine the exact amount of the mineral necessary for the improvement of plant and animal life. The time is regarded as ripe for beginning a system of study that will start with the soil and go right through to man. Those in charge of the project believe that the investigations will lead eventually to the production of foods which contain all the complex and subtly balanced nutrients which human beings need for sound health.

THE AMERICAN STANDARDS ASSOCIATION

THE American Standards Association has now completed its twenty-first year as central coordinating agency for the development of American industrial standards. During that time industry has used its facilities for the approval of more than four hundred standards, and some six hundred industrial and governmental groups have taken part in the work. American standards in engineering and allied fields have contributed greatly to our modern methods of production; and American standard safety codes have become the backbone of state industrial regulations for the protection of workmen.

Edmund A. Prentis, president of the association, speaking at this year's annual meeting, welcomed the following six trade and governmental groups that have affiliated with the association in the past twelve months. These are the American Association of Textile Chemists and Colorists; the American Institute of Architects; the American Welding Society; the Federal Works Agency; Modular Service Association, and a photographic group (consisting of the Agfa Ansco and Eastman companies). This brings the basic membership of the American Standards Association to seventy-three national trade associations, technical societies and governmental groups.

The advisory committee has been reorganized to include executives from industries not previously represented. The present committee consists of Howard Coonley, Ralph Budd, Floyd Carlisle, Karl T. Compton, Lammot du Pont, Lincoln Filene, Walter Gifford, Leroy Lincoln, J. H. McGraw, Jr., A. W. Robertson, Alfred Sloan, E. R. Stettinius and Walter Teagle.

According to the official announcement of the association, work undertaken during the year includes a program of standards for the prevention of occupational disease such as silicosis and other ills born of breathing air contaminated with toxic dusts and gases.

A new departure is the development of standards for photographic apparatus, supplies and equipment. Another project taken up during the year is standardization in the field of aeronautics. Last February representatives of the principal aeronautical organizations in this country met at the headquarters of the association to discuss the possibilities of national and international standardization of aircraft engines, aircraft and aviation fuels. In May, informal international conferences on these subjects were held in New York. The war situation in Europe, however, has brought international work practically to a standstill.

Perhaps the most important work completed during the year is the "American Standard Inspection Requirements for Motor Vehicles" developed under the supervision of the National Conservation Bureau and the American Association of Motor Vehicle Administrators.

Fourteen committees are working under the supervision of a Building Code Correlating Committee on a group of standards covering the entire field of the average building code. Another project has to do with coordination of dimensions of building materials and equipment, which it is hoped will encourage the application of new methods and processes that will lead to more economical housing. A number of projects have also been undertaken in the consumer field.

Officers of the association for 1940 are: Edmund A. Prentis, of the firm of Spencer, White and Prentis,

reelected president; R. E. Zimmerman, vice-president, United States Steel Corporation, reelected vice-president; R. P. Anderson, secretary of the division of refining of the American Petroleum Institute, elected chairman of the Standards Council; H. S. Osborne, engineer in charge of operating results of the American Telephone and Telegraph Company, elected vice-chairman of the Standards Council.

CONVENTION OF THE AMERICAN INSTITUTE OF ELECTRICAL ENGINEERS

THE winter convention of the American Institute of Electrical Engineers will be held in the Engineering Societies Building, New York City, from January 22 to 26.

The technical sessions will include papers on the following subjects: Electric Welding, Basic Sciences and Automatic Stations, Lightning Protection, Use of Radio for Airplane Navigation and Weather Forecasting, Circuit Breakers, Industrial Power Applications, Relays, Power Generation, Transportation, Electronics, Production and Application of Light, Power Transmission, Instruments and Measurements, Electrical Machinery, Insulation Co-ordination. There will be conferences on Electric Welding, Feedback Amplifiers, Networks, Sound, Test Code for Synchronous Machines, Transportation, the Use of Electronic Devices, Standards, Definitions.

On Wednesday evening, January 24, both the Edison and Hoover Medals will be presented in the Engineering Auditorium. The Edison Medal was awarded to Philip Torchio "for distinguished contributions to the art of central station engineering and for achievement in the production, distribution, and utilization of electrical energy." The Hoover Medal "awarded by engineers to a fellow engineer for distinguished public service" will be presented to Gano Dunn.

After the presentations a popular lecture on "Atomic Disintegration" will be delivered by Dr. Enrico Fermi, of Columbia University. His lecture will be followed by demonstrations of atomic disintegration by Dr. John R. Dunning. Dr. Fermi has been working with Dr. Dunning and the research group in physics at Columbia University, using the cyclotron in experiments on the physics of atomic nuclei.

Preceding the technical sessions on relays and communication on Tuesday afternoon a general session will be held for the presentation of the Alfred Noble Prize to Claude E. Shannon, of the Massachusetts Institute of Technology. He was awarded the prize for his paper entitled "A Symbolic Analysis of Relay and Switching Circuits."

Inspection trips of general interest will be available to members and guests attending the convention. The dinner honoring the "Outstanding Young Electrical Engineers" for 1939 will be held on Monday evening, January 22, at the Town Hall Club, New York. Larned A. Meacham, of the Bell Telephone Laboratories, Inc., New York, is the winner of the 1939 Eta Kappa Nu Award. Carl K. Gieringer, of the Liebel-Flarsheim Company, Cincinnati, Ohio, and Jesse E. Hobson, of the Westinghouse Electric and Manufacturing Company, E. Pittsburgh, Pa., will receive the Honorable Mention Award.

Following the convention there will be a post-convention cruise. The party will sail from New York at noon on January 27 on the *S. S. Robert Lee* and will return on the afternoon of January 30. It is planned to visit Williamsburg, Jamestown, Yorktown and Virginia Beach.

OFFICERS OF THE AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

A FULL account of the Columbus meeting of the American Association for the Advancement of Science and the scientific societies associated with it, edited by the permanent secretary, will be printed in the issue of SCIENCE for February 2.

Officers for 1940 were elected as follows:

President: A. F. Blakeslee, Carnegie Institution of Washington, Cold Spring Harbor, N. Y.

Vice-presidents of the association and chairmen of the sections:

Mathematics: A. B. Coble, University of Illinois.

Physics: A. L. Hughes, Washington University, St. Louis.

Chemistry: George Scatchard, Massachusetts Institute of Technology.

Astronomy: Robert R. McMath, McMath-Hulbert Observatory, Pontiac, Mich.

Geology and Geography: Hugh D. Miser, U. S. Geological Survey, Washington, D. C.

Zoological Sciences: L. J. Cole, University of Wisconsin.

Botanical Sciences: M. L. Fernald, Harvard University.

Anthropology: W. Duncan Strong, Columbia University.

Social and Economic Sciences: Holbrook Working, Stanford University.

Historical and Philological Sciences: Chauncey D. Leake, University of California Medical School, San Francisco.

Engineering: Robert L. Sackett, Pennsylvania State College.

Medical Sciences: Paul R. Cannon, University of Chicago.

Agriculture: W. H. Chandler, University of California at Berkeley.

Education: E. S. Ashbaugh, Miami University, Oxford, Ohio.

Members of the Sectional Committees:

Mathematics: J. L. Walsh, Harvard University.

Physics: George R. Harrison, Massachusetts Institute of Technology.

Chemistry: Ross A. Gortner, University of Minnesota.
Astronomy: D. B. McLaughlin, Observatory, University of Michigan.
Geology and Geography: John L. Rich, University of Cincinnati.
Zoological Sciences: H. H. Plough, Amherst College.
Botanical Sciences: W. J. Robbins, New York Botanical Garden.
Anthropology: Frank M. Setzler, U. S. National Museum.
Social and Economic Sciences: Stanley D. Dodge, University of Michigan.
Historical and Philological Sciences: Tenney L. Davis, Massachusetts Institute of Technology.
Medical Sciences: L. R. Dragstedt, University of Chicago.
Agriculture: W. A. Albrecht, University of Missouri.
Education: S. R. Powers, Teachers College, Columbia University.

Members of the Executive Committee of the Council (for four years beginning January 1, 1940): R. E. Clausen, University of California; Karl T. Compton, Massachusetts Institute of Technology.

Elected Members of the Council (for four years beginning January 1, 1940): Arthur H. Compton, University of Chicago; Austin H. Clark, U. S. National Museum.

Nomination to the Board of Trustees of Science Service (for three years beginning April, 1940): J. McKeen Cattell, Garrison, N. Y.

Member of the Finance Committee (for four years beginning January 1, 1940): Frederick P. H. Siddons, American Security and Trust Company, Washington, D. C.

Members of the Committee on Grants: S. A. Mitchell (for Astronomy), Leander McCormick Observatory, Charlottesville; J. T. Buchholz (for Botany), University of Illinois; Dayton C. Miller (for Physics), Case School of Applied Science, Cleveland (to succeed the late Dr. F. K. Richtmyer).

SCIENTIFIC NOTES AND NEWS

DR. J. C. ARTHUR, emeritus professor of botany at Purdue University, observed his ninetieth birthday on January 11.

THE Perkin Medal, awarded annually by the American Section of the Society of Chemical Industry "for valuable work in applied chemistry," will be awarded to Dr. Charles M. A. Stine, director of research and vice-president of E. I. du Pont de Nemours and Company, at a joint meeting, presided over by Wallace P. Cohoe, with the American Chemical Society, American Institute of Chemical Engineers, the Electrochemical Society and the Society of Industrial Chemistry at the Chemists' Club, New York City, on January 12. The program will be as follows: "The Life and Accomplishments of C. M. A. Stine"—Dr. Harrison E. Howe. Presentation of the Perkin Medal—Dr. Marston T. Bogert. "The Rise of the Organic Chemical Industry in the United States."—Dr. C. M. A. Stine.

DR. WILLIAM J. GIES, professor of biochemistry at Columbia University, received the achievement medal of the Alpha Omega Dental Fraternity at the close of its convention held in New York City on January 2. The presentation was made by Dr. Samuel Birenbach, of New York. Dr. Gies is editor of the *Journal of Dental Research.*

DR. ROBERT A. BUDINGTON, professor of zoology at Oberlin College, was honor guest at a testimonial dinner in Columbus on December 28. Former students, members of the Oberlin faculty and colleagues from the Woods Hole Marine Biological Laboratory were in attendance. Dr. Budington will retire this June.

FRIENDS and colleagues tendered a testimonial dinner on December 3 to Frank C. Caldwell, professor emeritus of electrical engineering at the Ohio State University, with which he has been connected since 1893.

DR. W. D. FUNKHOUSER, professor of zoology and anthropology of the University of Kentucky, head of the department of zoology and dean of the Graduate School, was elected at the Columbus meeting president of the Entomological Society of America.

AT a meeting on December 12 of the American Section of the Society of Chemical Industry, announcement was made of the resignation of Dr. D. D. Jackson, professor of chemical engineering and head of the department at Columbia University, who had served as president of the society for the past seven years. Officers for 1940 were elected as follows: *President,* Professor Henri Mouquin; *Vice-president,* Dr. J. V. N. Dorr; *Treasurer,* H. S. Polin; *Secretary,* Jerome Alexander; *Members of the Council,* L. H. Baekeland, L. W. Bass, Gerard J. Berchet, M. T. Bogert, J. L. Costa, Prosper Cholet, James H. Hibben, D. D. Jackson, John R. Johnson, W. A. Noyes, Jr., and Atherton Seidell.

DR. LEON WILSON HARTMAN, since 1909 professor of physics at the University of Nevada, was installed on December 15 as president of the university.

DR. EDGAR H. NORRIS, since 1938 professor of pathology at the College of Medicine at Wayne University, Detroit, has been elected dean of the college. He succeeds Dr. Raymond B. Allen, who recently became executive dean of the Chicago colleges of the University of Illinois.

DR. WILLIAM V. LAMBERT, in charge of investigations in genetics for the Bureau of Animal Industry of the U. S. Department of Agriculture, has been named associate director of the Agricultural Experiment Station at Purdue University, effective on February 1. He will have direct supervision of research. Professor Harry J. Reed, assistant director for twenty-two years, became in July dean of the School of Agriculture and director of the Experiment Station and of Agricultural Extension, succeeding Dean and Director Emeritus J. H. Skinner.

H. G. CHAMPION, of New College, has been appointed professor of forestry to fill the vacancy left at the University of Oxford by the death of Professor R. S. Troup.

DR. WALLACE J. ECKERT, assistant professor of astronomy at Columbia University, has been appointed director of the Nautical Almanac at Washington. He will assume his new duties in February.

DR. HUBLEY R. OWEN, chief surgeon of the medical division of the department of public safety of Philadelphia, has been appointed director of public health, succeeding Dr. Charles F. Nassau.

JEROME STRAUSS, vice-president of the Vanadium Corporation of America, has been elected a member of the Board of Directors of the American Standards Association to succeed Dr. G. W. Thompson, who recently resigned.

THE continuation of the study of bacteriophage at the University of California has been made possible by a grant of $2,430 from the John and Mary R. Markle Foundation, New York City. The research is being conducted by Dr. Albert P. Krueger, professor of bacteriology, who began the study while at the Rockefeller Institute for Medical Research.

THE state secretary of health of Pennsylvania, Dr. John J. Shaw, has announced the appointment of an advisory committee to assist in planning a program of tuberculosis control. Members of the committee are: Drs. Joseph McEldowney, John D. McLean, Louis Cohen, Charles J. Hatfield, Esmond R. Long, Burgess Gordon, Robert G. Torrey and William G. Turnbull, all of Philadelphia; Charles Howard Marcy, Pittsburgh; Charles H. Miner, Wilkesbarre; William Devitt, Allenwood, and John H. Bisbing, Reading.

DR. VANCE B. MURRAY, recently stationed in Berlin, and Dr. Herbert A. Spencer, who has been in Paris, both of the U. S. Public Health Service, have been sent to Finland at the request of the Finnish Red Cross.

J. FRANCIS MACBRIDE, associate curator of the herbarium of the Field Museum, after spending more than ten years in Europe, has returned. After a leave of absence he expects to return to his post at the museum later this year. Since 1929, when he went to Europe, Mr. Macbride has collected photographic negatives of more than 40,000 type specimens of plants, chiefly of South American species, preserved in the principal herbaria of various European countries. He has obtained also from the herbaria in Paris, Madrid, Vienna, Copenhagen and Geneva a large number of herbarium specimens.

DR. L. C. DUNN, professor of zoology at Columbia University, will deliver the fourth Harvey Society Lecture of the current series at the New York Academy of Medicine on January 18. He will speak on "Heredity and the Development of Early Abnormalities in Vertebrates."

DR. LUDVIG HEKTOEN, executive director of the National Advisory Cancer Council of the U. S. Public Health Service, will give the first of two annual Cutter Lectures in Preventive Medicine at the Harvard Medical School on January 15. He will speak on cancer control with special reference to its public health and epidemiologic aspects. Dr. James B. Murphy, of the Rockefeller Institute for Medical Research, New York, will give the second Cutter Lecture on January 22. He will give a critical review of experimental studies in cancer.

DR. WILLIAM ALLEN PUSEY, professor of dermatology emeritus in the College of Medicine of the University of Illinois at Chicago and past president of the American Medical Association, gave on January 9 under the auspices of the Institute of Medicine of Chicago a lecture entitled "High Lights in the History of Chicago Medicine" at a joint meeting of the Chicago Historical Society and the Society of Medical History of Chicago.

AT Cornell University, Dr. William F. Petersen, professor of pathology at the University of Illinois, gave on December 11 a lecture on the Schiff Foundation entitled, "Weather as It Affects Human Behavior." On December 15 Professor L. W. Ploger, of Syracuse University, described his "Experiences with the Seventeenth International Geological Congress in Russia in 1937."

DR. JOHN DEWEY, professor of philosophy emeritus, Columbia University, will give five lectures during the summer session from July 8 to 12 on the educational implications of current philosophical issues as part of a program entitled, "The Arts and Sciences To-day."

DR. HUGO ILTIS, formerly director of the Masaryk Volkshochschule in Brunn, now professor of biology in Mary Washington College at Fredericksburg, Va., proposes to establish there a Mendel Museum. He delivered a lecture on the "Life of Mendel" at Columbia University on December 7.

IN the article on "The Total D-amino Acid Content of Human Tumors and Normal Tissues," which appeared in the issue of SCIENCE for January 5, the name of the third author should be spelled Kabat and not Kabit.

THE annual meeting of the Society of American Bacteriologists, attended by over six hundred members of the society, was held in New Haven, Conn., from December 28 to 30, 1939. This was the fortieth anniversary of the founding of the society in the same city. Several of the charter members were present, and special recognition of the anniversary was made at the annual banquet and in a round-table discussion of the history of bacteriology, with special reference to the Connecticut valley.

A SERIES of lectures on medical care under the De Lamar Foundation of the School of Hygiene and Public Health of the Johns Hopkins University will be held on Tuesday afternoons at five o'clock from January 9 to February 2. The lecturers announced are: Dr. Nathan B. Van Etten, president-elect of the American Medical Association; Dr. E. S. Godfrey, commissioner of health of the State of New York; Dr. I. S. Falk, assistant director of the Federal Security Agency; Dr. R. C. Williams, chief medical officer of the Farm Security Administration; Dr. W. S. Rankin, director of the Hospital and Orphan Section of the Duke Endowment; J. D. Colman, director of the Associated Hospital Services of Baltimore; Dr. Kingsley Roberts, medical director of the Bureau of Cooperative Medicine, and Dr. Nathan Sinai, of the division of hygiene and public health of the University of Michigan.

THE new building for the Hall of Chemistry of the Oregon State College at Corvallis, which houses the laboratories of chemistry, chemical engineering and the department of agricultural chemistry of the Experiment Station, was dedicated on December 2. The building represents an expenditure of $425,000 and has been carried out under the P.W.A. Addresses were made at the scientific sessions by Dr. Linus Pauling, of the California Institute of Technology, and by Dr. Joel H. Hildebrand, of the University of California. The Hon. Willard L. Marks, of the State Board of Higher Education, presided. At the formal dedication the speakers included Governor Charles A. Sprague, Chancellor F. M. Hunter, of the State Board of Higher Education, and President George W. Peavy, of the college, and the Hon. Beatrice W. Sackett.

ORSON C. WELLS, a retired Chicago broker, who died on December 10, has bequeathed the bulk of his estate, said to be worth approximately $2,000,000, to the University of Chicago to found the Orson C. Wells Fund, for medical education and research in connection with the Billings Clinic, a part of the Albert Merritt Billings Hospital of the university. The gift will be used to meet the expenses of the medical work of the clinic. The will also provides for a bequest of $50,000 to the Presbyterian Hospital of Chicago for use in urologic research.

IT is announced that the Armour Institute of Technology and the Lewis Institute, both of Chicago, will be consolidated under the name of the Illinois Institute of Technology. Funds for an annual expenditure of $1,250,000 are available. Including evening institutes and community research services, an attendance of 7,000 was expected. For the present the work will be carried on jointly by the two institutes, but the acquisition of a new site is being considered.

THE Herman Knapp Memorial Eye Hospital of New York City, established seventy years ago, has become affiliated with Columbia Presbyterian Medical Center and Columbia University. The fixtures of the hospital will be moved to the Medical Center, and its activities and the care of out-patients will be resumed at the Medical Center by the Eye Institute and the Vanderbilt Clinic of the Presbyterian Hospital. Its assets will be taken over by Columbia University and will be administered as the Knapp Memorial Foundation in Ophthalmology for graduate study, teaching and research.

THE secretary of the Royal Academy of Italy, according to *Nature*, has announced that the Royal Academy of the Lincei has been amalgamated with the Royal Academy of Italy, which has taken over all the activities of the Lincei. As from July 1, 1939, the publications of the Academy of the Lincei will form part of the combined *Atti della Reale Academia d'Italia*, which will be divided into *Rendiconti* and *Memorie* of the class of moral and historical sciences and of the class of physical, mathematical and natural sciences. The publication of the *Notizie degli Scavi* will be continued without interruption by the Italian Academy. The Royal Academy of Italy will be pleased to send its publications to those institutions which received the publications of the Royal Academy of the Lincei under a system of exchange.

THE Lewis Cass Ledyard, Jr., Fellowship was established in 1939 by a gift from Mrs. Ruth E. Ledyard, wife of the late Lewis Cass Ledyard, Jr., a governor of the New York Hospital. The income, amounting to approximately $4,000 annually, will be awarded to an investigator in the fields of medicine and surgery in any closely related field, applied as follows: $3,000 as a stipend and, approximately, $1,000 for supplies and expenses. Preference will be given to younger applicants who are graduates in medicine and who have demonstrated fitness to carry

on original research of a high order. The research work under this fellowship will be carried on at the New York Hospital and Cornell University Medical College. The fellowship will be available on July 1 at the beginning of the academic year. Applications for the year 1940–41 should be addressed to The Committee of the Lewis Cass Ledyard, Jr., Fellowship, The Society of The New York Hospital, 525 East 68th Street, New York, N. Y., and should be in the hands of the committee by February 15. It is expected that the award will be made by April 1.

SEVERAL grants in support of medical research work have been received recently by the Medical School of the University of Minnesota. A gift of $5,000 has been made by Mrs. John Dwan, of St. Paul, to support the serum center which she had previously started with an endowment. From the John and Mary R. Markle Foundation $1,000 has been granted for work by Dr. Albert V. Stoesser, who is investigating water and electrolyte metabolism in tractable asthma. An annual grant for cancer research, made in the sum of $9,000 three years ago by the Citizens Aid Society of Minneapolis, has been increased to $10,000 a year for the next three-year period. The cancer research is being done by the departments of surgery, pathology and x-ray therapy in University Hospital. Minnesota also has received a fourth fellowship for special graduate training in cancer research from the National Cancer Institute. Another recent grant was that of $16,000 from the Barber Oil Company of Minneapolis to support investigations of the relation of diet and activity to cancer.

DISCUSSION

TWO PARADOXES

IN the archives of the Royal Society there are to be found a number of papers, many of which have never been published, showing that an animated discussion took place in the seventeenth century over the answer to this question: "Is the effect that can be produced by a moving body proportional to the first or to the second power of its velocity?" There were eminent names on both sides of this controversy, the followers of Descartes arguing for the first power, while Leibnitz led the opposition. The discussion was not purely theoretical in character, as each side could cite experimental evidence in support of its contention. An example stated in modern terms will make this clear.

A bullet is fired into a ballistic pendulum. If we focus our attention on the velocity imparted to the pendulum we find this to be proportional to the first power of the velocity of the bullet; but if we regard only the vertical height through which the pendulum is raised, this will be proportional to the second power of the velocity of the bullet.

Simple as this appears to-day, it was a real paradox two centuries ago, for though momentum (or quantity of motion) was a familiar idea to Descartes and Newton, the concepts of work and kinetic energy were yet over a hundred years in the future, and the discussion finally died out without reaching any decision.

It is instructive to note the way in which the nineteenth century finally resolved this paradox. The first step was a clarification of the question and a differentiation of the involved phenomena into two classes—momentum effects and energy effects, the latter class requiring the introduction of a new concept, which was so defined as to be consistent with previously existing mechanical theory. The rather vague ideas of Descartes and of Leibnitz assumed the forms of the conservation of momentum and the conservation of energy.

We have before us to-day a similar paradox dealing with the nature of the electron. Is it a charged particle or a little group of waves? And, as before, there is experimental evidence for both sides of the question. This is well brought out by the diffraction rings obtained by G. P. Thomson,[1] when negative electrons were shot through very thin films of metal. The electron must have a wave aspect, or there would be no interference pattern; it must also have a charged particle aspect, or the whole ring system would not be deflected by a magnet, as it is found to be. Perhaps the solution of this paradox, like that of the seventeenth century, will involve the same elements of clarification, differentiation and the introduction of a new concept.

PAUL R. HEYL
NATIONAL BUREAU OF STANDARDS

OXYGEN RELATIONS IN HYDROPHYTES

IT has been shown by experiments that the roots of willow cuttings obtain oxygen from two separate sources—the atmosphere of the soil and from the shoot.[1] That the roots of herbaceous hydrophytes may also use internal (photosynthetic) oxygen as well as atmospheric oxygen is suggested by certain features of habit and structure.

The root systems of herbaceous hydrophytes are, in a very large number of species, adventitious, arising from some type of underground stem, as rhizomes. Among plants with root systems which are formed

[1] G. P. Thomson, *Proc. Roy. Soc.*, 117: 600, February 1, 1928.
[1] W. A. Cannon, *Plant Physiol.*, 4, 1932.

on rhizomes is *Carex limosa,* or mud sedge, of northern America and Europe. (Other species of sedge which occur in acid-free substrata have similar root systems).

The rhizome of *C. limosa* is long, branched and has long internodes.[2] It is superficially placed in the substratum. The most striking structural feature is the internodal development of large chambers, which, in effect, are storage chambers for gases, especially for oxygen.

The adventitious root system is dimorphic, consisting of adventitious or main roots which are relatively slender and much branched, and main roots which are relatively thick and which may or may not bear laterals. There are, thus, really two kinds of thick roots, branched and not branched. The slender and thicker main roots have unlike origins. The slender roots arise at the base of flower shoots; the thicker roots are formed at the base of leafy shoots.

Root hairs occur abundantly on nearly all the roots. The thicker main roots have aerating tissue composed of 10 to 15 rows of intercellular spaces, arranged radially.

It has been observed (Metsävainio) that the roots with prominent intercellular spaces may penetrate deeply; those without it are usually superficial. The crucial structural difference between the two is evidently the presence or the absence of aerating tissue.

It will be recalled that other herbaceous hydrophytes also have well-developed intercellular spaces or chambers, for example, Elodea and Equisetum. Those of the former may, when the plants are in sunshine, contain much oxygen, derived from carbon assimilation. And, in certain scouring rushes the air chambers are the most prominent features both of the shoot and of the rhizome. It is because of this that the rhizome, as in *E. fuviatale,* may penetrate deeply in a wet, or saturated substratum. An analogous condition appears to obtain in some sedges which have aerating tissue not only in the rhizomes but also in the thicker main roots, and the origin of these roots at the base of the leafy shoots has, from this point of view, great significance. They may also be storage organs for oxygen, especially oxygen of internal origin.

From these and other considerations it is concluded that the slender and much branched main roots, without prominent intercellular spaces, and which are shallowly placed, derive the oxygen they require from the well-aerated soil atmosphere immediately around them. It, in fact, is because of this readily obtainable oxygen that these roots have laterals. The thicker main roots, on the other hand, which have aerenchyma, develop and live where the oxygen supply is limited, but they are able to secure the necessary amount from the rhizome and/or chlorophyll-bearing shoot. It is because of this that they live under poor conditions of aeration in spite of the relatively small water-absorbing and *oxygen*-absorbing surface.

W. A. CANNON

STANFORD UNIVERSITY

[2] K. Metsävainio, *Ann. Bot. Soc. Zoolog.-Bot. Fennicae Vanamo,* 1. Helsinki. 1931.

HARDINESS OF THE PAPER-MULBERRY TREE

A TREE that supplies paper to part of Asia and materials for clothing to many Pacific islanders was formerly much planted in the United States.

This curious tree *Broussonetia papyrifera* Vert. is said to be hardy up to New York City and also to sometimes escape and spread, naturally, though the sexes are in separate trees. "Is the female of the species more tender than the male"? was a question not to be answered by the Arnold Arboretum, as outside the climatic limit of this tree. Possibly some reader of SCIENCE may know the answer.

In Baltimore, Md., many of these trees flourished in yards, being introduced by Jesuit Fathers, it is said. But as far as known all the trees here are staminate or male and not capable of colonizing new localities. Yet in North Carolina one sees the strange flowers and the mulberry-like fruit that might spread seed to new regions. In Florida also female trees are found.

When, on different occasions, little female trees from Florida were planted in Baltimore, they flourished exceedingly all summer, but failed to survive the winter, as the male trees do.

It may be that this tree is exceptional and that both sexes are not equally hardy and thus the limits of its natural distribution would be set by one sex while artificially by man the other sex may be grown over a wider area. Is there such a physiological difference?

E. A. ANDREWS

JOHNS HOPKINS UNIVERSITY

THE GALTON LABORATORY

YOU were good enough (November 10) to reprint for the information of readers of SCIENCE, the letter of protest which I wrote to the London *Times* on the obstacles placed in the way of the Galton Laboratory continuing its researches. It is now possible to give a somewhat fuller view of the situation.

Many of the constituent institutions of London University are again active. The London School of Hygiene and Tropical Medicine, for example, situated only a few hundred yards from University College, along Gower Street, has its library and main departments open. I have been unable to ascertain, even if undergraduate teaching is supposed to be safer elsewhere, why research departments should be forbidden to continue at University College, which now stands nearly empty.

The Galton Laboratory has established its right to continued existence, though it has been forced to leave London. Sir John Russell was kind enough to find it

space at Rothamsted, and the college has withdrawn its ban on the attendance of my assistants. Apart from small sources of income, such as the sale of mice, we must rely on the income of Francis Galton's trust, and this will suffice to make sure that the work he initiated will be continued.

It has been suggested to me that many American friends, who would be glad, from time to time, of statistical assistance and advice, have refrained from writing in the belief that I should be too busy. This is not so. I should, indeed, be glad to earn some support for my department by such professional services. Any sympathizer who considers that we could supply assistance worth $100 towards his own researches is invited to put up a problem; though I must add that I should be sorry if this offer were to prevent any friend, who might otherwise write to me for advice, from doing so as freely as before.

R. A. FISHER

ROTHAMSTED EXPERIMENTAL STATION,
HARPENDEN HERTS, ENGLAND,
GALTON LABORATORY

QUOTATIONS

CHEMISTRY IN THE SERVICE OF THE STATE[1]

I HAVE been invited to represent the State of Oregon in this dedicatory exercise. This building, erected under state auspices as an important structure on the campus of this state college, may appropriately claim the attention of the chief executive. So I bring you greetings in my official capacity, and tender my congratulations on this consummation of the hopes of the scientists and administrators connected with this institution and the state system of higher education.

Your committee on arrangements has appropriately planned a symposium to-day, with learned scientists invited as participants, in which certain phases of this great science of chemistry are being discussed. In such a forum I am not qualified to take part. In fact, as a representative of the political agency I appear here with a certain sense of humiliation. I realize that from time immemorial the political arm has seized the knowledge of the experimenter and the scientist for ignoble ends. This is particularly true of chemistry and its ally, physics. From the days of the crude catapult, from the time when Greek fire was used to destroy the enemy ships about Byzantium, from the time when the new mixture of saltpeter, charcoal and sulfur was used to hurl missiles with death-dealing force, down to the present day with its high explosive shells, its poison gas, its armored tanks and flying bombers, government has used the discoveries of science in the business of warfare and the killing or mutilation of enemies. To-day it almost seems as if government leers over the shoulder of the patient chemist and urges him to compound some deadlier substance for the destruction of his fellowmen. In this respect Dr. Faustus remains the symbol of chemistry: with all its aspiration to conquer matter in the service of mankind, its soul remains in pawn to the devil. For organized society persists in devoting the discoveries of science to diabolical designs; or ignores the evil consequences which attend the application of such discoveries.

The central problem of our time becomes therefore not so much scientific as ethical and philosophic. How can we employ the products of science for beneficent ends! Science itself is amoral. It is the use made of science which determines its moral coloring. The potion which Friar Lawrence gave to Juliet was only a soporific, from which after two and forty hours she would "awake as from a pleasant sleep." The dram which Romeo forced the hungry apothecary to sell him was so potent a poison that "if you had the strength of twenty men it would dispatch you straight." But in the complexities of modern life the line of demarcation between the good and evil uses of scientific discoveries is not so clear as between the harmless sleeping potion of Juliet and the deadly poison of Romeo. A new machine or a new compound creates social as well as economic reactions. Therefore as the scientist reveals more the secrets of nature and points the way to their utilizations, the philosopher, the economist, the moralist, the statesman must labor alongside of him lest man become the victim of his own intelligence.

I have one more thought. You here dedicate a building to a use. May I as governor of this state dedicate it to a principle: the fearless search for truth. That is a concession the political arm is sometimes loath to give, for usually government seeks to keep its branches subservient to the regime. Yet if there is anything which modern science stands for it is the quest for truth. In spite of resistance sometimes clerical and sometimes political that quest has proven its virtue. Now generally accepted in the field of the natural sciences, that principle meets opposition at times in its extension to the area of social relationships. Yet it is in this field there now are occurring those gropings which often eventuate in new experiments or new discoveries.

Let this building stand dedicated to the service of

[1] Address of the Honorable Charles A. Sprague, governor of Oregon, at the dedication of the new Chemistry Building of the Oregon State College at Corvallis.

science through search for truth in an atmosphere of freedom. The gnawing of the elements in this climate will eventually wear away this structure of brick and concrete. But if the climate of liberty is preserved, truths will here be revealed which will live on and on. I trust they will serve not only to gratify intellectual pride, but may, through beneficent and wise application, work for the betterment of man.

SCIENTIFIC BOOKS

THE LIFE AND LETTERS OF LORD RUTHERFORD

Rutherford: Being the Life and Letters of the Rt. Hon. Lord Rutherford, O.M. By A. S. EVE, C.B.E., D.Sc., LL.D., F.R.S. Pp. xvi + 451. New York: The Macmillan Company; Cambridge, England: The University Press. 1939. $5.00.

THIS important book, written by so close an associate of Rutherford as was the author, will be read with the greatest of interest by physicists. Rutherford's influence extended beyond the domain of his science, so that his life is one of moment to the layman as well as to the specialist. However, while there are many sections of the book which will appeal to those who fall in the former category, the greater part of the contents is such as will be comprehended only by the professional man of science. It is not implied that the work contains profound or abstract material. It is composed very largely of letters and accounts of scientific achievements which, while simple in form of presentation and of outstanding interest for the physicist who knows what they are about, are apt to form rather dull reading for the ordinary layman.

Some of the most interesting and informative letters are those written in Rutherford's student days to the lady who was afterwards to become his wife. They are surprisingly detailed. They cover descriptions of everything and everybody, and in them one sees the young Rutherford working out the details of his finances, his hopes for their improvement and his general plans and ambitions for the future. In some cases he becomes quite technical, describing his apparatus and experiments in some detail, so that one almost gets the suspicion that he is conserving time and effort in combining into what should have been a love letter the opportunity of writing up his notes. The letters portray, as might be expected, a prodigious energy and an unfailing confidence in ultimate success, together with a continual aliveness to the essentials necessary to secure it, not only in the scientific, but also in the diplomatic and economic domains.

Rutherford's early life in New Zealand is interesting as foreshadowing the career that was to come, and perhaps we see in embryo an element of that resourcefulness of later years embodied in one of his own stories of this period:

> My mother sent me out to bring the cow home to the paddock and to collect some fire wood as well. So I drove the cow and pulled a big branch of a tree behind me. Then I thought, why shouldn't the cow help me? So I tied the branch with a rope to the end of her tail and she went quietly home till she came to a narrow gate. Here the branch jammed and the last bit of her tail broke off!

We find him as a boy making cameras, taking clocks to pieces and making water-wheels, as did Newton. Later, as a student at Canterbury College, we find him already engaged upon his work on the magnetization of iron by high-frequency discharges, which was later to provide his first claims to recognition when, as an 1851 Exhibition scholar, he continued his work at Cambridge, England.

Rutherford came to Cambridge at a transitional period, at a period when the scholar of the old school was dominant in the halls of learning and when scientific research was only beginning to come into its own for recognition. A degree for research had just been established, and Rutherford was the first research student to arrive in this category. We learn how one or two demonstrators with ancient prejudices that no good things came from the Colonies were wont to pass the door of his laboratory with a sneer, until he politely asked them in, told them he was in some difficulties with his experiments, and sought their advice, with the resulting complete collapse of their dignity and profundity; for they quickly realized that they had not the faintest shadow of a notion of what he was doing. That Rutherford was not long in establishing himself in the esteem of his surroundings is borne out by a remark of Dr. Andrew Balfour to the effect that "We've got a rabbit here from the Antipodes and he's burrowing mighty deep."

At Cambridge we have a picture of the development of his young student life, of his rapid incorporation in the community of the active investigators who resided in or visited Cambridge, of the growth of those elements which cemented his plans for the future, and withal, of the beneficent and almost fatherly interest in him shown by his great master, J. J. Thomson. Last but not least, we see a story so typical of one destined to blaze new trails in science. We see young Rutherford continuing, carrying to success, and even to the point of the attainment of considerable reputation, a field of activity—his work upon magnetic detectors, and the like—which, while worthy in itself,

was obviously bounded in its limitations. We sense the gradual recognition of this boundary and the diversion of interest to other fields, in particular, to those having to do with the conduction of electricity through gases, and finally we see the crystalization of interest upon the embryo of that special field—radioactivity—which was to form the main part of Rutherford's life work.

Following Cambridge, the picture turns to McGill, where Rutherford was called to succeed H. L. Callendar. Hardly could one find two men so different in their lines of work and even in their personalities. Callendar was a distinguished representative of the age of highly accurate thermal measurements. He was one of those who kept physics alive in this field at a time when there rang continually in the ears of the investigator the lament of that distinguished German scholar who had so recently maintained that all the important things in physics had been done and that little remained but to improve upon former work and add an extra decimal here and there. The work of Callendar concerned the one or two parts in ten thousand type of investigation, and in it he had justly attained a preeminence which established for his work the highest respect everywhere and in McGill in particular. Moreover, he was a man of quiet personality and apt to mingle but little with those around him. Then came Rutherford, with an entirely new type of apparatus, a type so characteristic of the newly born school of atomic physics. The high precision potentiometers were replaced by crude electroscopes made out of mustard cans. Pumps and sealing wax appeared everywhere, and one per cent. was a good limit of accuracy. Many of the methods used in the new field were representative, as viewed through the spectacles of the old realm of accurate measurement, of all that they should not be. It is natural that there should have been a period during which the new professor, so confident in his course, so energetic in his attack and so unconventional in his methods, should be regarded with uncertain appreciation and with some doubts as to the soundness of his reasoning. His rapid elucidation of the facts of radioactivity, and the thoughts revolutionary to the ideas of the day thereby established, raised conditions in which colleagues in other departments of the university gravely expressed the fear that the radical ideas about the spontaneous transmutation of matter might bring discredit on McGill University. At one open meeting of the McGill Physical Society, Rutherford was indeed criticized in this way and advised to delay publication and proceed more cautiously. That his McGill critics were not alone, however, is borne out by the remarks of other pillars of science of this period. We see the great Lord Kelvin suggesting that radium receives its energy "by absorption of ethereal waves" and that gamma rays are simply vapors of radium, while alpha rays are atoms of radium bromide. Professor H. E. Armstrong expresses himself "astonished at the feats of imagination to which he had listened" and leans towards Lord Kelvin's view of an "external source of energy." Rutherford's attitude towards some of these views is indicated rather clearly by a letter to his wife written in 1904, in which he writes: "Lord Kelvin has talked radium most of the day, and I admire his confidence in talking about a subject in which he has taken the trouble to learn so little."

It was, of course, at McGill that Rutherford's most pioneering work in radioactivity was done. It was while here that he built up his great friendships with Boltwood and Bumstead. It was at McGill that he collaborated with Soddy, and it was soon after the assumption of his professorship here that he married.

On the retirement of Professor Schuster from Manchester, Rutherford accepted a call to the chair and returned to England, where the rest of his life was spent. We read of his adjustment to the new conditions, a characteristic clash with the professor of chemistry who, before his arrival, had annexed certain of the rooms which previously belonged to physics, a clash which ended in his pursuit of the said professor to his study protesting that he was a nightmare—"like the fag-end of a bad dream."

Rutherford was always particularly outspoken, and perhaps one might say that diplomatic tact was not a distinguishing characteristic. It is, therefore, inevitable that two such forceful presonalities as Rutherford and Ramsay, each with his own particular branch of science claiming ownership of the new field of radioactivity, should come frequently into controversy, almost to the point of acrimony. Perhaps the general attitude may be summed up in a single paragraph of one of Boltwood's letters to Rutherford written from Yale. He writes:

> I write with some feeling on this matter because I had a devil of a time trying to persuade some of my chemical friends last summer that Ramsay was not the whole show in radioactivity. We had a general meeting of the American Chemical Society here in New Haven at the end of June and practically every mother's son that I met was firmly convinced that Ramsay was the biggest thing that could be seen on the horizon. Practically not a single one was willing to concede that he even "might be wrong." I did not attempt to persuade them that he *was* wrong, but only attempted to prepare their minds for the denials of his conclusions which I felt sure would be forthcoming. I think that most of them felt the same sort of pity for me that a good catholic feels for one who is not a true believer. For the Pope can do no wrong.

In view of the foregoing situation, it is natural

that we should find considerable trouble with Sir William Ramsay over the relative apportionment between the two investigators of the radium which was allotted for their use by the Kaiserliche Akademie der Wissenschaften of Vienna. However, the work proceeds with ever-increasing acceleration, the further unravelling of the details of radioactive phenomena and the determination of radioactive constants adding prestige to Rutherford's name, until he was rewarded in 1908 by the receipt of the Nobel Prize.

It was while at Manchester that Rutherford developed his ideas concerning the existence of a central atomic nucleus of small size. We read of his various contacts with colleagues the world over, of his interest in public affairs, and then of that period during the great World War in which, of course, much of his attention was devoted to war work. It is interesting to note that even during this period of stress, we find communications going on in friendly spirit between Rutherford and some of his former collaborators who were then in the ranks of the enemy. It would indeed be difficult to make a war out of such men, if they alone peopled the lands of the earth.

When Sir J. J. Thomson retired from the Cavendish professorship at Cambridge, England, Rutherford was the natural successor, and he accepted the appointment in 1919. Sir J. J. Thomson became Master of Trinity, but still retained some activities as professor of physics without stipend "with rooms and mechanics essential to the continuance of his research work." It is not unnatural to find Rutherford's dominant personality, coupled with J. J. Thomson's long control of affairs, the cause of some little necessity of adjustment. But all was soon amicably settled, and Rutherford drafted a statement by way of agreement. It is quoted as one "full of alterations, erasures, additions, all uninitialled; it was a document which would make a lawyer weep, but there are the initials at the bottom, J.J.T., E.R. It was sufficient; it worked."

We may sense Rutherford's impulsive yet humorous attitude from the following quotation concerning a conversation with his well-known assistant, Crowe: "Now, Crowe, have some mica absorbers ready tomorrow with stopping power equivalent to 50 cm of air." "Yes, sir." On the next day: "Now, Crowe, put in a 50 cm screen." "Yes, sir." "Why don't you do what I tell you—put in a 50 cm screen." "I have, sir." "Put in 20 more." "Yes, sir." "Why the devil don't you put in what I tell you—I said 20 more." "I did, sir." "There's some damned contamination." "Put in *two* 50's." "Yes, sir." "Ah, it's all right; that's stopped 'em! Crowe, my boy, you're always wrong until I've proved you right! Now we'll find their exact range!"

In treating of the period at Cambridge, the author naturally covers at the same time the history of the main developments which the Cavendish Laboratory brought forth during what is approximately the last twenty years of Rutherford's life. There are accounts of the famous experiments on nuclear disintegration by alpha particles, of the disintegration of matter by artificial means, of the discovery of the neutron, of the work of Kapitza and of Aston. We read of his increasing responsibilities and distinctions, and the book, after reviewing the circumstances attending his last illness, concludes with a brief summary of his achievements and a list of his honors.

We can, perhaps, conclude this review no better than by citing the following characterization of Rutherford quoted by the author from *Nature* (19 July, 1906):

> His own successes as an investigator may be traced to a few well-marked characteristics. The first is his pertinacious and reiterated assault at the particular point which he wishes to attack. He has also an instinctive insight which often makes his initial point of view more trustworthy than the deliberate conclusion of some befogged experimenter. Most noteworthy of all is the extreme simplicity and directness of his experimental methods. Some observers seem to grow happier as their apparatus becomes more complex.

Professor Eve has produced a work dealing with the life of one of the most distinguished men in all the history of science, a work which teems with interest for the physicist, both as a chronicle of achievement and as a picture of the personality of the central figure.

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SPECIAL ARTICLES

STUDIES ON THE FATE OF PLASMA PROTHROMBIN[1]

THE published studies on the metabolism of plasma prothrombin have been directed only at its site of formation; no report has described its site of destruction. That plasma prothrombin is being continuously destroyed in, or lost from, the circulating blood is indicated[2] by following the level in the blood after

[1] This study was carried out under a grant from the John and Mary R. Markle Foundation. From the Department of Surgery of the New York Hospital and Cornell University Medical College, New York.

[2] W. DeW. Andrus, J. W. Lord, Jr., and R. A. Moore, "The Effect of Hepatectomy on the Plasma Prothrombin and the Utilization of Vitamin K." *Surgery*, Vol. 6: 899–900, Dec., 1939.

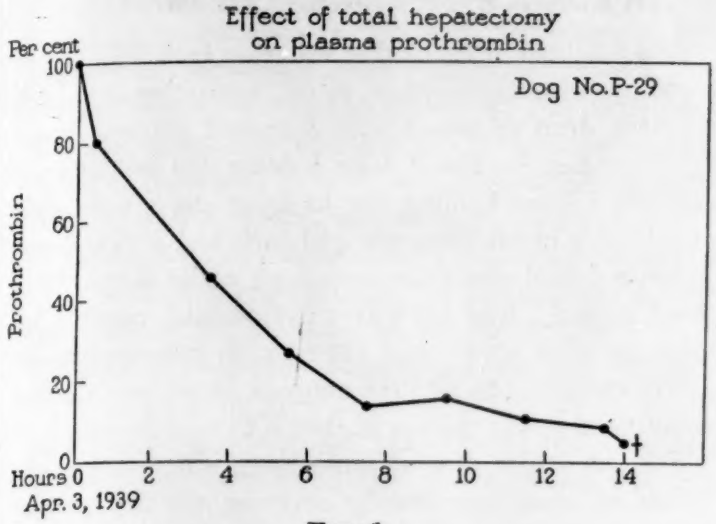

FIG. 1

total hepatectomy in the dog. The characteristic curve of plasma prothrombin after total hepatectomy (Fig. 1) shows a rapid fall to 50 per cent. of the pre-operative level three hours after operation, and a more gradual fall to approximately 5 per cent. of normal by the fourteenth hour post-operatively. Other experiments have shown that this fall is in no way altered when massive doses of vitamin K and bile salts are injected into the small intestine at the time of operation. These experiments suggest the following conclusions: first, that the liver is the sole site of formation of plasma prothrombin; second, that the liver forms this substance continuously; and third, that plasma prothrombin disappears rapidly and continuously from the circulating blood. It was in an effort to find the site of this loss of plasma prothrombin that the present work was undertaken.

METHOD

Healthy mongrel dogs weighing between 10 and 20 kilo. were used in all experiments. Nembutal anesthesia was employed, supplemented by intratracheal insufflation when thoracotomy was necessary. Samples of blood were taken from the afferent and efferent vessels of the head, lung, liver, spleen, intestine, kidney and hind limbs. Samples from the right and left ventricles of the heart were used to test the values of plasma prothrombin in the blood before and after passing through the pulmonary circuit. The plasma prothrombin content was determined by the method of Warner, Brinkhous and Smith.[3]

RESULTS

The plasma prothrombin levels in the samples of blood before and after passing through the lungs showed the only consistent and significant differences. The values for the arterial and venous blood of other organs were the same—within the limits of our experimental error. The limit of error of the Warner, Brinkhous and Smith test in our hands is 3 per cent. when the blood samples are run at one sitting, as in these experiments. In 17 (85 per cent.) of 20 animals the plasma prothrombin level was from 4 to 19 per cent. lower in the blood from the left ventricle than in that from the right ventricle. In the other three experiments, the values were the same from both sides of the heart. The average loss of prothrombin, in passage through the lungs, was 10.6 per cent. in the 17 animals that showed a difference in levels. This was in marked contrast to the results obtained in series involving the other organs, in which no significant differences were found.

In order to rule out oxygenation of the blood as a factor in the destruction of prothrombin, the following experiments were performed. In four dogs blood samples from the right ventricle were divided into two parts through one of which oxygen was bubbled, and a sample of blood was taken from the left ventricle of each dog at the same time. In no instance did oxygenation change the plasma prothrombin content of blood from the right ventricle, yet the plasma prothrombin content of the left ventricle blood was, on the average, 6.5 per cent. lower in this group. Further, exposure of citrated blood samples to air for as long as six hours failed to cause any change in the prothrombin content.

In one experiment, after removing blood samples from each ventricle, the left main bronchus was tied off, causing complete atelectasis of the left lung. After a lapse of 20 minutes, determinations of plasma prothrombin showed the same degree of fall (17 per cent.) in the samples removed from the circulation of each lung. This difference in plasma prothrombin was identical with that of the samples taken before initiation of atelectasis.

DISCUSSION

These results point to the lungs as the site of disappearance of plasma prothrombin. The question arises as to the factor or factors involved in the decrease of this substance as the blood passes through the pulmonary circuit. Two mechanisms are theoretically possible: first, oxygenation of the blood may cause a decrease of plasma prothrombin; and second, a specific tissue substance may be responsible. That the first mechanism is not the explanation has been shown not only by the results of bubbling oxygen through blood without changing its plasma prothrombin content, but also by the fact that blood circulating through an atelectatic lung loses an amount of plasma prothrombin comparable to that lost in passage through a normally aerated lung. Evidently, simple elevation of the oxygen content of blood does not destroy plasma prothrombin. The second idea, that

[3] E. D. Warner, K. M. Brinkhous and H. P. Smith, *Am. Jour. Physiol.*, 114: 667–675, 1936.

a specific tissue component is involved, is supported by certain experimental data.

Thus Howell and Donahue[4] have advanced evidence to show that blood platelets are formed in capillaries of the lung, and are being discharged continuously into the blood stream. In 15 (88 per cent.) of 17 experiments they have found the number of platelets in the blood from the left side of the heart to be greater than in that from the right side of the heart, and that the increase averaged 13.3 per cent. in the 15 successful experiments. Further proof was adduced by perfusion experiments and by histological examination of the lung. In our experiments the lowering of the level of the plasma prothrombin as blood passes from the right to the left side of the heart by way of the pulmonary circuit corresponds both in frequency and in degree to the increase in blood platelets found by Howell and Donahue. The platelets disintegrate and in so doing, liberate thromboplastin. According to the present accepted mechanism of blood-clot formation, the action of thromboplastin and calcium on prothrombin changes it to thrombin. Platelets are the chief source of intravascular thromboplastin; they are fragile and are continuously undergoing disintegration. Loss of prothrombin is then dependent upon the thromboplastin and calcium. This mechanism accounts for the continued loss of prothrombin after the source of supply, the liver, has been removed.

SUMMARY

The level of the plasma prothrombin in the circulating blood is decreased during its passage through the pulmonary capillaries. In 85 per cent. of samples, plasma prothrombin has been found to be less in the blood of the left ventricle than in that from the right ventricle. This difference averaged 10.6 per cent. and ranged from 4 to 19 per cent. In no instance was the level in the right ventricle lower than that in the left. In samples of blood taken from the arterial and venous supply of the head, liver, spleen, intestine, kidney and hind limbs, no significant difference in plasma prothrombin levels was found.

A possible explanation of this role of the lung in the loss of plasma prothrombin is thought to be the production of blood platelets in this organ, as demonstrated by Howell and Donahue. Platelets, as they undergo disintegration, initiate the first stage of the clotting process by releasing thromboplastin, which, in the presence of calcium, changes prothrombin to thrombin.

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[4] W. H. Howell and D. D. Donahue, *Jour. Exp. Med.*, 65: 177–203, 1937.

IMPEDANCE OF BIMOLECULAR FILMS

BIMOLECULAR films having water on both sides[1] were made by bringing together, in oil, a hanging drop and a sessile drop of water with a tanned protein monolayer on each.[2] The J tube holding the sessile drop and the I tube holding the hanging drop were each about 1 cm inside diameter and each had a cylindrical platinized lead electrode 1 cm long about 2 mm from the film end. The oil was amyl acetate, purified by shaking with water and filtering to remove surface active constituents, and the aqueous phase was a dilute solution of tannic acid in M/100 KCl acidified to about pH 3. A stable film of tanned egg albumin was obtained at each interface by carrying the dry powder through the oil on a moistened glass fiber. After the two monofilms were brought together, the resistance decreased as the intervening oil was forced out and did not reach a constant value for several hours.

Alternating current impedance data were obtained on one film as described and on a second in which lecithin was added to the oil before the films were brought together. There were only minor differences between these data. The impedances were measured with a Wheatstone bridge over the frequency range from 30 to 200,000 cycles per second.[3] The data of the second experiment have been plotted[4] as series resistance, R_s, *vs.* series reactance, X_s, in Fig. 1. The

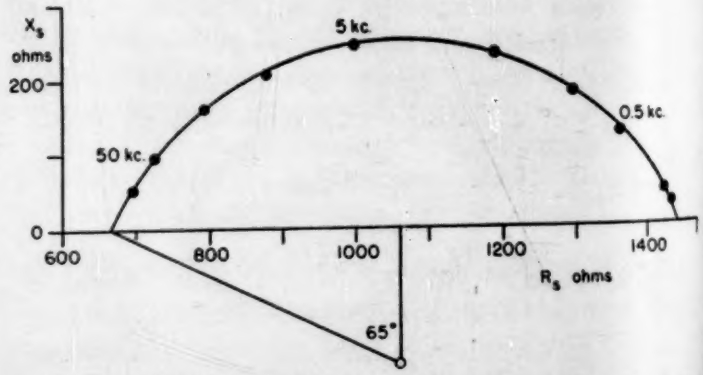

FIG. 1. Impedance locus, series resistance, R_s *vs.* series reactance, X_s, of a bimolecular tanned egg albumin and lecithin film. The frequencies indicated are in kilocycles per second. The film had an area of 0.07 cm², 790 ohms direct current resistance, 65° phase angle and 0.086 microfarads capacity at 1 kilocycle per second.

extrapolated infinite frequency resistance, R_∞, is the resistance of the electrolyte between the electrodes and the film. The difference between the extrapolated zero frequency resistance, R_o, and R_∞ is the direct current resistance of the film. From the film areas of

[1] R. B. Dean, *Nature*, 144: 32, 1939.
[2] J. H. Schulman and E. K. Rideal, *Proc. Roy. Soc.* B, 122: 29 and 46, 1937.
[3] K. S. Cole and H. J. Curtis, *Rev. Sci. Inst.*, 8: 333, 1937.
[4] K. S. Cole, *Jour. Gen. Physiol.*, 15: 641, 1932.

approximately 0.07 cm² these film resistances were found to be 94 and 52 ohm cm², respectively. The changes of impedance with frequency between these two limits were due to the capacitative impedances of the films, which had constant phase angles of 68° and 65° and capacities of 1.07 and 1.23 microfarad/cm² at 1,000 cycles/second, respectively.

The resistance of these films is in marked contrast to the extremely low resistances found in untanned protein films.[1] This reopens the possibility that complex lipo-protein films may have an appreciable resistance and be able to produce diffusion potentials in biological systems. The constant phase angle and a capacity of about one microfarad/cm² is a striking characteristic of all living cell membranes so far measured[5] and we believe these to be the first artificial films produced between two aqueous phases which had these properties.

One of us (R.B.D.) wishes to thank Columbia University and the Marine Biological Laboratory for their hospitality while doing this work.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

MASS PRODUCTION OF VACCINE AGAINST TYPHUS FEVER OF THE EUROPEAN TYPE

IT is unnecessary to emphasize the importance at the present time of the development of prophylactic vaccination against typhus fever. Until 1925, it was supposed that immunization against the Rickettsiae diseases was possible only as a result of actual infection. Since then, however, various attempts to employ living, supposedly attenuated virus for prophylactic purposes have been made[1,2]—all of them, in our opinion, dangerous both for the individual and for the community. Spencer and Parker (1925)[3] were the first to demonstrate that active immunization against spotted fever could be achieved with killed, phenolized Rickettsiae obtained from infected ticks. Following this (1930), Weigl[4] reported analogous results with phenolized European typhus Rickettsiae harvested from the intestinal contents of lice artificially infected. Subsequently (1930), one of the writers with Batchelder[5] and then with Castaneda[6,7] and Macchiavello[8] demonstrated that active immunization against the murine and the European varieties of typhus fever could be produced in animals with formalinized suspensions of the respective micro-organisms. The principles were thus established, but difficulties still remained in the way of obtaining the relatively large amounts of Rickettsiae necessary for practical immunization. Numerous reports have been made by investigators who claim to have been able to cultivate Rickettsiae on media without tissue. The present writers, however, because of the negative results reported by other workers and their own failure, after long experience and persistent effort in similar attempts, feel that, up to the present, such tissueless cultivation of virulent Rickettsiae has not been achieved.

We may summarize the present state of affairs in regard to typhus vaccine production as follows:

As far as the murine variety of typhus fever is concerned, tissue culture methods of various kinds are easily carried out. By none of these procedures can such large quantities of Rickettsiae be produced as by the technique of intraperitoneal inoculation of x-rayed rats, a method sufficiently described in preceding communications. As first developed by one of us with Castaneda,[9] this method has been utilized in its original form and with modifications on a considerable scale by Castaneda in Mexico and Veintemillas in Bolivia.

Unfortunately, the rat methods have, in the course of years of effort, proved inapplicable to the classical European virus. In consequence, other procedures have been suggested.

The Weigl louse technique is effective, but entirely unsuitable for large-scale application.

Tissue culture methods based on the modified Maitland technique as first developed for European Rickettsiae by Nigg and Landsteiner[10] were used for immunization, first, by Kligler and Aschner[11] and

[1] Blanc, *Bull. Soc. Path. Exot.*, 311, 1916.
[2] J. Laigret, R. Durand and J. Belfort, *C. R. Acad. des Sci.*, 202: 519, 1936.
[3] R. R. Spencer and R. R. Parker, *U. S. Publ. Health Rep.*, 40: 2159, 1925.
[4] R. Weigl, *Bull. Acad. Polonaise des Sci. et des Lettres*, Classe Med., 25, 1930.
[5] H. Zinsser and A. P. Batchelder, *Jour. Exp. Med.*, 51: 847, 1930.
[6] H. Zinsser and M. R. Castaneda, *Jour. Exp. Med.*, 53: 493, 1931.
[7] H. Zinsser and M. R. Castaneda, *Jour. Exp. Med.*, 57: 381, 1933.
[8] H. Zinsser and A. Macchiavello, *Jour. Exp. Med.*, 64: 673, 1936.
[5] K. S. Cole, Tabulae Biologicae, Cellula (in press).
[9] H. Zinsser and M. R. Castaneda, *Proc. Soc. Exp. Biol. and Med.*, 29: 840, 1932.
[10] C. Nigg and K. Landsteiner, *Proc. Soc. Exp. Biol. and Med.*, 28: 3, 1930.
[11] I. J. Kligler and M. Aschner, *Brit. Jour. Exp. Path.*, 15: 337, 1934.

were enlarged for greater quantity production by one of the writers with Macchiavello.[12] While immunologically valid and quantitatively more useful than the Weigl method, the Maitland technique still remains inadequate for large-scale work.

Recently, two further techniques have been described. The first of these is our own agar tissue procedure which, now adapted to use with Kolle flasks, furnishes considerable amounts of vaccine;[13,14] the second is the Cox method of inoculation of fertile hen's eggs.[15] In 1934[16] Dr. Zia demonstrated in our laboratory that European and murine Rickettsiae would grow on the chorio-allantoic membranes of hen's eggs, but the yield was too small for practical purposes. Cox inoculated directly into the yolk sac. Microscopically, he finds few if any Rickettsiae of various types in the chorio-allantois and in tissues of the embryo itself. In the yolk sacs, however, Rickettsiae are numerous with the spotted fever and murine typhus infections, though none were found in the European variety of typhus.

We have repeated the Cox method, using the European strain, and have passed the virus to date through 15 egg passages. The embryos die regularly after 4 days. After several passages, we begin to find Rickettsae in the yolk membranes, although they are rarely very numerous. We have never found Rickettsiae in the embryos themselves. Comparisons between the egg method and our own agar technique indicated that, as far as yield of active material was concerned, the two procedures were of the same order, although the yolk membranes of the eggs infected with the European virus titrated somewhat higher in guinea pigs than did the material from the agar tubes—in the proportion of about 10^{-7} to 10^{-6}. There are, however, some advantages in the agar method, such as greater ease of cellular elements from the vaccine and more accurate morphological control.

The method which we now employ to secure large numbers of Rickettsiae consists in a combination of the agar method—using considerably enlarged surfaces for cultivation—and the egg technique as a source of inoculum. Specifically, the minced embryonic tissue or macerated yolk sac taken from eggs on the fourth day following infection is used to inoculate large quantities of normal minced chick tissue from 10-day embryos. The tissue thus infected is distributed in large amounts on the agar surfaces of modified Kolle flasks. The neck of the ordinary flask is replaced by one which will receive a No. 6 rubber stopper. After 6 or 7 days' incubation at 37° C., cultures very rich in Rickettsiae are obtained. We emphasize the fact that considerable quantities of tissue may be employed. Transplants can then be made by using the culture Rickettsiae or new cultures inaugurated with material from infected eggs.

By this method, with a personnel of one bacteriologist and two technicians, one liter of vaccine sufficient for 300 complete immunizations can be produced in a week. Increase of production is only a matter of enlarging equipment and personnel.

Since embryonic mouse tissue has also been used successfully in the agar method, it could be substituted for the chick material. For the present, however, the latter gives excellent yields and has proved satisfactory.

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[12] H. Zinsser and A. Macchiavello, *Proc. Soc. Exp. Biol. and Med.*, 35: 84, 1936.
[13] H. Zinsser, H. Wei and F. FitzPatrick, *Proc. Soc. Exp. Biol. and Med.*, 37: 604, 1937.
[14] H. Zinsser, F. FitzPatrick and H. Wei, *Jour. Exp. Med.*, 69: 179, 1939.
[15] H. R. Cox, *U. S. Public Health Rep.*, 53: 2241, 1938.
[16] S. Zia, *Am. Jour. Path.*, 10: 211, 1934.

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